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ANNALS OF INTERNAL MEDICINE

VOLUME 21 AUGUST, 1944 NUMBER 2

GLYCOSURIA IN MENINGITIS *

By FRANK FERGUSON, M.D., and DAVID BARR, M.D., F.A.C.P.,
New York, N. Y.

SINCE 1884 [1] there have been in the literature scattered references to the occurrence of glycosuria in meningitis. Some have been in the form of case reports, and in several emphasis has been placed on the rarity of the association. Our interest in the subject was excited by the admission to the New York Hospital of a comatose woman of 41 with signs both of meningitis and of diabetic coma. Therapy begun simultaneously for both conditions

TABLE I

Etiology	Total Cases	No Glycosuria	Initial Glycosuria with Previous History of Glycosuria	Post-Infusion Glycosuria	Unexplained Initial Glycosuria
Meningococcus	26	14	1	2	9
Pneumococcus	8	3	1	3	1
Staphylococcus	8	4		2	2
Lymphocytic chorio meningitis	3	2		1	
Streptococcus	2	1		1	
E. coli	1	1			
H. influenzae	2	2			
Tubercle bacillus	6	4		1	1
Syphilis	3	2		1	
Mumps	2	2			
Toxoplasma	1	1			
Unknown	10	6		3	1
Total	72	42	2	14	14

resulted in uneventful recovery from the meningitis and in the prompt disappearance of glycosuria. A study of this case led to a review of the records of patients admitted to the New York Hospital during the preceding four years, with the specific purpose of determining the incidence of glyco-

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suria or other evidences of disturbed carbohydrate metabolism in the course of meningitis.

Records were found of 72 cases of meningitis, 30 of whom showed glycosuria. Fourteen of the 30 cases had received infusions of dextrose solution at some time before the appearance of glycosuria. In the remaining 16 cases, cause for the glycosuria other than the meningitis itself was not immediately evident. In table 1 the cases of meningitis are listed according to their etiology. Table 2 displays certain details of the 16 cases which had unexplained glycosuria. Further details of these cases are presented in the following summaries.

TABLE II

Case No.	Sex	Age	Causative Organism	Glycosuria		Acetonuria		Initial Blood Sugar	Initial C.S.F. Sugar	Initial CO_2	Insulin Units	Previous Evidence Diabetes
				Maximum	Duration Days	Maximum	Duration Days					
1	F	8	Meningococcus	++	2	+	3	155	103	29	0	No
2	F	36	Meningococcus	++	2	++	1	153	10	54	0	No
3	M	34	Meningococcus	++	2	++	2	244	3		0	No.
4	M	6	Meningococcus	++++	3	++	1		5		0	No
5	F	18	Meningococcus	++	1	++++	2		0		75	No
6	M	16	Meningococcus	+++	1	0		122	0		0	No
7	F	19	Meningococcus	++	1	0		150	26		0	No
8	M	47	Meningococcus	++++	10	++	1	209	110	69	20	No
9	F	26	Meningococcus	+++	3	+++	3	212	10		0	No
10	F	18	Meningo-coccus—?	+++	3	++	3		59		0	No
11	M	4	Pneumococcus	++++	3	++	3		51	48	0	No
12	F	13	Staphylococcus	+	2				59		0	No
13	M	49	Staphylococcus	++	1						0	No
14	M	43	Tubercle	+	1				0		0	No
15	F	57	Pneumococcus	++	6	++++	1		140		900	Yes
16	F	41	Meningococcus	++++	2	++	1	441		14	245	Yes

Case 1. A girl of 8 one year before entering the hospital had a urine examination which was negative for sugar. She was admitted after a few hours of fever, headache, vomiting, delirium, and semi-coma. Examination revealed numerous petechial spots, a stiff neck, strabismus, drowsiness, hyperactive reflexes, and bilateral positive Babinski reflexes. At the time of admission her blood sugar was 155 mg. per cent, CO_2 capacity 29 vol. per cent, white blood cells 21,300. Cerebrospinal fluid was cloudy with 11,000 white blood cells, Pandy 3 +, sugar 103 mg. per cent. Meningococci were cultured from both blood and spinal fluid. She was treated with sulfadiazine for 13 days. On the second day her urine showed a trace of sugar and a faint trace both of acetone and of diacetic acid. The CO_2 capacity had risen to 53 vol. per cent. On the third day there was still a faint trace of acetone but thereafter the urine was normal. The temperature became normal on the fourth day, the leukocyte count on the fifth day. Blood sugar was 96 mg. per cent, the blood culture was negative and the cerebrospinal fluid had become almost normal on the seventh day. Convalescence was uneventful and she was discharged without symptoms on the fifteenth day. Two months later she was reported to be entirely well.

Case 2 was a woman of 36, whose urine examination two years before had been entirely negative. She was admitted to the hospital following a week of upper res-

piratory infection, two days of muscle aching, chills and restlessness, and a few hours of headaches, vomiting and stiff neck. On examination she was semi-comatose with a temperature of 40° C., signs of meningeal involvement and a hemorrhagic rash. Examination of her urine showed sugar 2 +, acetone 2 +, diacetic acid 4 +, leukocytes 9,900, fasting blood sugar 153 mg. per cent, CO_2 capacity 54 volumes per cent. The cerebrospinal fluid contained 36,000 white blood cells and had a sugar content of 10 mg. per cent. Meningococci were cultured from the spinal fluid. She was treated with sulfadiazine, intravenous glucose, and sodium bicarbonate. The meningeal signs cleared in a few days. On the second day, urine sugar was 2 +, acetone 0, diacetic acid 2 +. The urine was negative thereafter. She appeared to be completely well at the time of discharge from the hospital. Seven months later she was in robust health without residuals and with no signs of diabetes. Glucose tolerance tests * were as follows:

	Fasting	½ hr.	1 hr.	2 hr.	3 hr.
5th day	86	176	208	160	
6th day	81	185	175	202	116
Urine sugar	0	0	0	0	0
7 mos. later	85	158	125	83	78
Urine sugar	0	0	0	0	0

Case 3 was a man of 34 who two weeks before entry to the hospital had a mild upper respiratory infection. One week previously he had developed muscle aches, a transient pin-point rash, and chilly sensations. For two days he had been drowsy and had suffered from anorexia. Vomiting started one day before admission with headaches and increasing stupor. Examination revealed a temperature of 38.3° C., stupor, dehydration, slight strabismus, and signs of meningeal involvement. Urine examination revealed sugar 2 +, acetone 2 +, diacetic acid 4 +. Blood sugar was 244 mg. per cent. The leukocyte count was 26,000. The cerebrospinal fluid contained 25,000 leukocytes and 3 mg. per cent of sugar. Gram negative diplococci were seen on smear. He was treated with sulfadiazine and sodium bicarbonate. On the second day the urine sugar was 1 +, acetone 1 +, diacetic acid 1 +. Thereafter the urine was normal. On the second day the cerebrospinal fluid sugar had a value of 74 mg. per cent. On the fourth day he was asymptomatic. His convalescence was entirely uneventful. Sugar tolerance tests were as follows:

	Fasting	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.
13th day	84	142	122	108	76	85
Urine sugar	0	0	++++	0	++++	0
8 mos. later	88	155	131	92	103	
Urine sugar	0	0	±	0	0	

Case 4 was a boy of 6, whose urine had been negative for one year before admission. He came into the hospital after two days of fever, malaise, vomiting, neck pain and delirium. Examination showed a temperature of 38.2° C., dehydration, opisthotonos, petechial spots and moderate signs of meningeal involvement, urine sugar 4 +, acetone 2 +, diacetic acid 2 +. He was treated with sulfadiazine and intravenous glucose and with paraldehyde as a sedative. On the third day his urine showed a trace of sugar but was normal thereafter. Meningococci were cultured from the cerebrospinal fluid which had a sugar content of 5 mg. per cent. He recovered

* Unless otherwise specified sugar tolerance tests were performed after the administration of 100 grams of glucose by mouth.

and was discharged on the eighteenth day. His condition appeared to be entirely normal on the follow-up examination which, however, included no special studies of his carbohydrate metabolism.

Case 5. A girl of 18 had had an upper respiratory infection for 11 days and fever, headache, vomiting, and rather severe muscle pain for 24 hours. Her examination revealed a temperature of 42.5° C., dehydration, restlessness, semi-coma, injected pharynx, and signs of meningeal involvement. Urine examination showed sugar 2 +, acetone 4 +, diacetic acid 1 +, leukocyte count was 33,100; blood cultures were negative. Meningococci were cultured from the spinal fluid which contained 23,100 leukocytes but no sugar. She was treated with infusions and with doses of regular insulin amounting to 75 units in the first five hours. Her urine was clear after six hours except for a trace of acetone on the second day. She received sulfadiazine or sulfamethazine for a period of 10 days. After the seventh day she was asymptomatic except for bilateral seventh and ninth nerve palsies which had started on the second day. Sugar tolerance on the twelfth day was:

	Fasting	1 hr.	2 hr.	3 hr.
Blood sugar	90	127	136	114
Urine sugar	0	+	0	0

She was discharged on the fifteenth day and one and a half months later had no signs of paralyses. Four months later she appeared to be entirely well except for sinusitis.

Case 6 was a boy of 16, who one day preceding his admission to the hospital became irrational with fever, headache, chills and vomiting. Examination revealed temperature of 42.4° C., conjunctivitis, signs of meningeal involvement and semicoma. Examination showed urine sugar 3 +, acetone 0, diacetic acid 1 +, leukocyte count 25,200, blood sugar 122 mg. per cent, blood culture negative. Meningococci were cultured from the cerebrospinal fluid which contained 15,000 leukocytes. The sugar content of the fluid was too low to read. He was treated with sulfadiazine for eight days. The urine became negative on the second day and he was asymptomatic after the seventh day. He was discharged from the hospital as cured on the sixteenth day. Nine months later there were no residuals of meningitis and no signs or symptoms of diabetes. Sugar tolerance tests were as follows:

	Fasting	½ hr.	1 hr.	2 hr.	3 hr.
2 mos. later	89	96	85	70	101
9 mos. later	98	130	70	70	69

Case 7. A girl of 19 ten days before entry had had chills, fever, malaise, and a petechial rash. The eruption disappeared after about two days. Three days before entry she suffered from shaking chills, fever and headache. For one day she had had vomiting, stiff neck, drowsiness, increasing headache and a skin rash. Examination revealed a temperature of 37° C., blood pressure 110 mm. of Hg systolic and 70 mm. diastolic, an erythematous eruption and signs of meningeal involvement, urine sugar 2 +, acetone 0, diacetic acid 0, leukocyte count 20,000, blood sugar 150 mg. per cent, negative blood cultures. Meningococci were cultured from the cerebrospinal fluid which contained 23,000 leukocytes and 26 mg. per cent of sugar. She was started on sulfadiazine but because of hematuria was shifted after 24 hours to sulfamethazine which was continued for a period of 10 days. The urine was negative on the second day and remained so thereafter. She herself was asymptomatic after the fourth day.

Her convalescence was uneventful, and she appeared to be entirely well one month after her discharge from the hospital. Sugar tolerance tests were as follows:

	Fasting	½ hr.	1 hr.	2 hr.	3 hr.
5th day	77	212	268	211	74
Urine sugar	0	0	++	+++	+++
13th day	85	127	150	117	145
Urine sugar	0	+	+++	++	0

Case 8 was a man of 47, who for two weeks had had an upper respiratory infection. For 24 hours he had had headache, profound weakness, and increasing stupor. At the time of admission he was semicomatose and had a petechial eruption. His thyroid was diffusely enlarged and the liver could be felt five fingers'-breadth below the costal margin. There were definite signs of meningeal involvement. His blood pressure was 185 mm. of Hg systolic and 105 mm. diastolic and the temperature was 38.3° C. Urine examination revealed sugar 4 +, acetone 2 +, diacetic acid 4 +. Blood sugar was 209 mg. per cent. Meningococci were cultured from the cerebrospinal fluid which contained 9,900 leukocytes and which showed 4 + Wassermann reaction. He was treated with sulfadiazine for 11 days. The meningeal signs had disappeared by the tenth day. The cell count and Wassermann reaction in the spinal fluid were normal on the seventeenth day. Acetone had disappeared from the urine on the second day but glycosuria continued from 2 + to 4 + for eight days, was negative on the ninth day, 2 + on the tenth and negative thereafter. During this period it was suspected that he might be diabetic. Insulin was given tentatively in doses of 10 units on the sixth and seventh days of his illness but was discontinued thereafter. On the seventeenth day liver function tests revealed no abnormalities and his basal metabolic rate was plus 2. At the time of his discharge from the hospital he had entirely recovered from the meningitis. His thyroid gland and his liver were enlarged as at the time of admission. Two weeks later his urine was found to contain 3 + sugar. Five months after discharge no sugar or acetone was demonstrable. Three months after leaving the hospital he was employed as a dishwasher and was able to continue this work without special treatment and with no recognizable signs or symptoms of diabetes. The sugar tolerance tests were as follows:

	Fasting	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.
4th day	182	212	280	313	330	322
Urine sugar	0	0	++		++++	
12th day	124	241	270	320	224	133
Urine sugar	0	0	++	+++	+++	0
29th day	119	202	280	295	189	

Case 9 was a woman of 26 who for two days had suffered from muscle pains, headache, and fever and for 24 hours, from vomiting. Examination showed disorientation with temperature of 38.9° C., hemorrhagic rash and signs of meningeal involvement. Urine showed sugar 3 +, acetone 3 +, diacetic acid 0. Blood contained 31,000 leukocytes and 212 mg. per cent of sugar. Blood cultures were negative. Meningococci were grown from the cerebrospinal fluid which contained 31,000 leukocytes and 10 mg. per cent of sugar. The Wassermann reaction was 4 + in the first spinal fluid but gradually became less positive and finally negative in subsequent examinations. She was treated with sulfadiazine for 12 days. On the second day the urine showed sugar 4 +, acetone 3 +; on the third day, sugar 2 +, acetone 2 +

but neither sugar nor acetone thereafter. Weakness of the left lateral rectus muscle started on the third day but gradually disappeared. She was discharged on the sixteenth day without symptoms except for a diplopia which persisted for two months. Six months later she showed no signs of diabetes, no weakness of the extraocular muscles. There was, however, a fine tremor of the hand; her pulse rate was 92 under resting conditions; she had rapid changes in mood and was easily irritated. Her appetite was very vigorous and she gained 16 pounds during the six months following her discharge. Graves' disease was suspected and she was given iodine therapeutically for a period of 4 months, without change in her state. At no time did she develop the eye signs of hyperthyroidism; the thyroid gland was never enlarged. Sugar tolerance tests were as follows:

	Fasting	½ hr.	1 hr.	2 hr.	3 hr.
11th day	90	207	208	134	122
Urine sugar	0	+	+++	++	0
14th day	98	173	190	131	100
Urine sugar	0	0	0	0	0
6 mos. later	104	182	161	114	61
Urine sugar	0	+	++	0	0

Case 10. A girl of 18 had suffered for two days from fever, chilly sensations, and cough. Examination showed a temperature of 39.2° C., blood pressure of 108 mm. of Hg systolic, 64 mm. diastolic, signs of a pneumonia at the right lower lobe and no meningeal signs. Urine sugar was 3+, acetone 2+, diacetic acid 1+. The leukocyte count was 7,100 and cultures of the blood were negative. The cerebrospinal fluid was clear, contained 1 cell and 80 mg. per cent of sugar. She was treated with sulfadiazine and infusions and was given paraldehyde as a sedative. Twelve hours after admission her neck became stiff and she developed positive Kernig and Brudzinsky signs. Her spinal fluid contained 19,000 leukocytes with a 4+ Pandy and a sugar content of 59 mg. per cent. On the second day her urine showed sugar 3+, acetone 2+, diacetic acid 0; on the third day, 3+ sugar, 2+ acetone. Thereafter it was negative. The meningeal signs cleared in a few days and the pneumonia resolved on the eleventh day. She was discharged without symptoms. Two and a half months later she felt well and had no signs of diabetes. Her sugar tolerance at that time was as follows:

	Fasting	½ hr.	1 hr.	2 hr.	3 hr.
2½ mos. later	104	178	100	94	94
Urine sugar	±	0	±	±	0

Possibly because of early sulfonamide treatment all cultures were negative both in blood and spinal fluid. Although the etiological agent was not determined the case was considered, because of its clinical picture, one of meningococcemia with later development of meningococcic meningitis.

Case 11 was a boy of 4, who for four days had had headaches with fever, loss of appetite and vomiting and for one day dyspnea, projectile vomiting and convulsions. At the time of admission paraldehyde and ether anesthesia were required for control of violent spasms. He had signs of meningeal involvement and a right flaccid paralysis of the face and body. Urine sugar was 4+, acetone 2+, diacetic acid 0. Pneumococcus Type XVIII was cultured from the spinal fluid which contained 2,600 leukocytes and 51 mg. per cent of sugar. Blood cultures were negative.

He was treated with sulfadiazine, infusions, and type XVIII horse serum. The urine showed sugar 2 +, acetone 1 +, on the third day but was normal thereafter. On the ninth day the skull plate showed signs of increased intracranial pressure and mastoiditis. On the twelfth day he was asymptomatic except for right hemiparesis and aphasia. Sulfadiazine was discontinued on the sixteenth day. On the twentieth day he spoke a little and the paralyses were less marked. He was discharged on the forty-ninth day with only partial paralysis of the right arm. One and a half years after his acute illness he had attacks suggestive of petit mal and had developed spastic paralysis with contractures in the right arm. He was otherwise well. No urines were obtained but no signs or symptoms of diabetes were noted.

Case 12. A girl of 13, with staphylococcic meningitis, had a faint trace of sugar in the urine during the first two days of her illness. There was no previous history of diabetes or of glycosuria and no other data concerning carbohydrate relationships were obtained. She died on the third day of observation.

Case 13. A man of 49, with staphylococcic meningitis, brain abscess and empyema had a trace of sugar in his urine during the first day in the hospital. No other observations on carbohydrate metabolism were made before his death on the fifth day.

Case 14. A man of 43, with tuberculous meningitis, had a faint trace of sugar in his urine on the first day following his entry to the hospital. Two months previously his blood sugar level had been found to be 71 mg. per cent. No observations were made on his blood sugar or other carbohydrate relationships during the four days intervening between his entry and his death.

Case 15 was a woman of 57 who six weeks before admission had had a nasal catarrh, gradual loss of hearing, tinnitus, and pain in the left ear. The local doctor found only slight injection of the drum and no mastoid pain. Four weeks before she was admitted to the hospital her physician discovered glycosuria with a blood sugar of 186 mg. per cent. He treated her with 10 units of protamine insulin each day and with a diet containing 70 grams of protein, 100 gm. of fat, and 200 gm. of carbohydrate. During a period of six months she had lost about 30 pounds. For two weeks before her entry to the hospital she had suffered from increased thirst and slight pruritus vulvae and for one day with chill, fever, increasing pain in the left ear and a stiff neck. Examination revealed a temperature of 40.6° C., dehydration, stiff neck, left purulent otitis media, acetone breath, drowsiness, and signs of meningeal involvement. The urine sugar was 2 +, acetone 4 +, diacetic acid 3 +. Blood culture was negative and leukocytes were 14,800. Pneumococcus Type III was cultured from the spinal fluid, which had a 1 + Pandy and contained 3,500 leukocytes and 140 mg. per cent of sugar. She was treated with sulfadiazine, with intravenous glucose, and insulin. During the first 11 days the dosage of insulin varied from 35 units to 95 units. It was then reduced to 15 units and so continued for 13 days. Myringotomy yielded only one small drop of pus. A simple mastoidectomy performed on the second day showed extensive mastoid necrosis with dural involvement. At that time her urine still showed 4 + sugar but no acetone. On the third day cultures of the cerebrospinal fluid were negative, the patient felt much improved with a glycosuria of 2 +. She was asymptomatic on the sixth day with urine sugar 2 +, blood sugar 103 mg. per cent. Thereafter only slight traces of sugar were found. On the ninth day an attack of dizziness was attributed to a hypoglycemic reaction although the blood sugar on that morning had been 242 mg. per cent. On the eleventh day the blood sugar was 202 and on the sixteenth day 190 mg. per cent. On the twenty-fourth day she was depressed and agitated and it was thought that the insulin dosage might be contributing to her mental state. Insulin was discontinued and thereafter she remained completely well with no glycosuria and with no further need of insulin. On the twenty-seventh day her blood sugar was 146 mg. per cent, and on the thirty-seventh day sulfadiazine was discontinued. She was discharged without

symptoms on the forty-sixth day. Ten months later she had taken no insulin, had gained 19 pounds, and had eaten an unrestricted diet without excessive appetite, polydipsia, polyuria or pruritus vulvae. She felt entirely well except for slight left mastoid pain and a continuous tinnitus of a totally deaf left ear. Repeated urine examinations by her home physician showed no sugar. Her sugar tolerance at this time, however, was as follows:

	Fasting	½ hr.	1 hr.	2 hr.	3 hr.
	184	259	360	396	315
Urine sugar			+++	++++	++++

Case 16 was a woman of 41 who had had three previous admissions to the hospital. The first, 18 months previously, had been for the treatment of pernicious anemia and bronchiectasis. During her stay in the hospital she showed on several occasions traces of sugar in her urine. The second admission nine months previously was because of a pneumococcus Type III infection of the mastoid. During the first 10 days of this period her urine contained sugar in amounts varying from 1 + to 4 +. Her admission sugar, however, was only 96 mg. per cent and a glucose tolerance on the eleventh day was within normal limits:

Fasting	½ hr.	1 hr.	2 hr.	3 hr.
90		140	150	69

Her third admission was for plastic closure of the mastoid, and at this time she showed no glycosuria. Her fourth admission had been preceded by one day of fever, chills, joint pains, vomiting, rash, headache, and stiff neck. Examination revealed a temperature of 39.4° C., blood pressure of 88 mm. Hg systolic and 58 mm. diastolic, slight cyanosis, opisthotonos, hemorrhagic skin eruption, and signs of meningeal involvement. She was in deep coma and had a strong acetone breath. Urine sugar was 4 +, acetone 2 +, diacetic acid 4 +, blood sugar 441 mg. per cent, CO_2 combining power 14 vol. per cent, calcium 10 mg. per cent. Blood cultures were positive for meningococcus, which was also found on smear of the cerebrospinal fluid. The leukocyte count in the fluid was 1,800. She was treated with sulfadiazine, intravenous glucose, M/6 molar sodium lactate and 245 units of insulin in 12 hours. At the end of the first day her urine was negative, her blood sugar was 33, the CO_2 combining power 66. Insulin was discontinued. On the second day the urine sugar was 2 +. Thereafter the urine was normal. She was asymptomatic on the seventh day and was discharged as cured. Thirteen months later it was found that her anemia was poorly controlled and that her teeth were troubling her. She had no signs or symptoms of diabetes. On the twentieth day and again 13 months later intravenous sugar tolerance test with 50 c.c. of 50 per cent glucose revealed the following:

	Fasting	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.
20th day	73	192	114	77	53	78
Urine sugar	0	++++	0	0	0	0
13 mos. later	118	175	86	63	76	
Urine sugar	0	+++	+	0	0	

She was seen in the outpatient department 16 months after discharge from the hospital without symptoms of diabetes and without glycosuria.

Comment

Of the 16 cases exhibiting glycosuria without obvious explanation, three died during the acute stage of the disease and observations were too limited to permit opinion whether the glycosuria was a concomitant of the meningitis or an evidence of some more long standing disturbance in the carbohydrate metabolism. Twelve of the 16 (1–11, 16) appeared at some interval after the subsidence of acute symptoms to be entirely free from any clinical evidence of diabetes. In six of the 12 (2, 3, 6, 9, 10, 16) this impression was confirmed by sugar tolerance curves which could be considered within normal limits. In three of the 12 cases no sugar tolerance curves were obtained after the subsidence of the acute illness. In three cases there was a question of a previous or accompanying diabetic or prediabetic state. Those cases require some further comment and analysis.

In case 8 the glycosuria persisted for 10 days and then ceased. Sugar tolerance curves taken on the fourth, twelfth, and twenty-ninth days, however, were abnormal. Furthermore glycosuria was demonstrated two weeks after the patient's discharge from the hospital. Five months later there was no sugar or acetone in the urine and the patient was working regularly without symptoms and without recourse to insulin. Unfortunately no sugar tolerance curves could be obtained at that time. In spite of these later observations indicating freedom from clinical diabetes, the possibility of a more or less permanent defect in the carbohydrate metabolism could not be excluded, and it was thought that the patient might have been suffering from a prediabetic condition which was exacerbated by the acute illness. That the abnormal sugar tolerance curves and the recurrent glycosuria were not due to the enlarged thyroid is indicated by a normal basal metabolic rate. The possibility that the enlargement of the liver was due to hemochromatosis was considered but could not be proved.

Case 15 presented a most interesting problem. She had exhibited glycosuria and had been treated for diabetes before the onset of her meningitis. This difficulty had begun two weeks after an otitis media and preceded by four weeks the onset of the meningitis. The diabetic state appeared to be exaggerated by the meningitis, and for a time doses of 35 to 95 units of regular insulin were required for its control. Following mastoidectomy, however, her condition rapidly improved. The glycosuria disappeared and it did not recur when insulin was discontinued. Ten months later she was symptom-free on an unrestricted diet without insulin. At that time, however, her fasting blood sugar was still 186 mg. per cent and the curve of blood sugar following the ingestion of glucose revealed a diminished tolerance. It seemed necessary to conclude that this patient was a mild diabetic in whom otitis media, mastoiditis and meningitis produced a temporary exacerbation.

It was case 16 that originally attracted our attention to the question of glycosuria in meningitis. During two of her previous admissions—one for

pernicious anemia and bronchiectasis, and the other for a pneumococcal infection of the mastoid—sugar had been found in her urine. This might have been regarded as evidence of diabetes if a sugar tolerance test during one of these admissions had not been within normal limits and if in the intervals she had not been quite free from symptoms suggesting the disease. The clinical picture at the onset of meningitis mimicked diabetic coma with 4 + sugar, 4 + diacetic acid, blood sugar 441 mg. per cent, and CO_2 capacity 14 vol. per cent. Dosage of 245 units of insulin during the first 12 hours was thought to be necessary. By the second day, however, insulin was discontinued, and the urine remained normal thereafter. Sugar tolerance curves were normal on the twentieth day and again 13 months later. Doubt must be entertained concerning the diagnosis of diabetes in this patient although the frequent glycosuria is evidence of an easily induced disturbance of carbohydrate metabolism.

Case 10 deserves comment for a different reason. At the time of admission, she was suffering from a generalized infection thought but not proved to be meningococcal septicemia. Glycosuria was present at this time. It was not until 12 hours later that signs of meningitis developed. Glycosuria was not notably increased after the meningitis became evident.

Discussion

This study reveals that glycosuria is by no means an infrequent accompaniment of the onset of meningitis. Of 32 cases, 16 showed sugar in the urine. Of these three may have been diabetic or pre-diabetic. In the remainder the glycosuria was unexplained. The phenomenon was encountered in meningitis due to meningococcus, pneumococcus, staphylococcus, and the tubercle bacillus. It was also found in one case of acute meningitis in which the etiology was not established. The meningococcic cases constituted by far the greatest number of the series, and of the 26 examples of meningococcic infection more than one third (34.6 per cent) showed unexplained glycosuria.

Of the 13 glycosuric cases in which tests for acetone and diacetic acid were made ketosis was demonstrated in 11. There was no constant relationship between glycosuria and the presence of ketone bodies in the urine. In two cases of glycosuria acetone was not demonstrated and in several with 4 + sugar reactions the ketosis was mild. Furthermore among the 44 cases which showed no glycosuria, 10 exhibited ketone bodies in appreciable amounts.

Usually the glycosuria was transient. It disappeared in all the cases and persisted beyond the third day in only three of the 16.

The literature concerning glycosuria in meningitis consists for the most part of reports of scattered cases and of experiences with small groups. It embraces examples of meningitis of the most diverse etiology. One of the earliest articles was that of Frew and Garrod,[2] who reported 41 cases of

tuberculous meningitis, in 15 of which marked glycosuria was demonstrated. In 11 others the urine partially reduced Fehling's solution. They found glycosuria a late manifestation, and in most of their cases sugar appeared within the last 48 hours of life. Nohecourt [3] reported a case of tuberculous meningitis in which vomiting and acetonuria were followed by the appearance of moderate amounts of sugar in the urine. Another case of tuberculosis of the meninges studied by Krafchik and Slobody [4] exhibited glycosuria at the onset of the infection. Stupor with urinary sugar 4 +, acetone 3 +, blood sugar 200 mg. and CO_2 combining power 36 vol. per cent led to the diagnosis of diabetic coma. Treatment with insulin which corrected the glycosuria and ketonuria and caused a hypoglycemic reaction did not control the stupor, thus permitting recognition of the meningitis.

Glycosuria without ketosis in a 40 year old man with pneumococcus Type II meningitis was reported by Roussel.[5] Although the later condition of the patient is not described, it is inferred that there was no suspicion of permanent diabetes.

Taylor and McKinstry [6] reported a case of suppurative meningitis which developed in the course of pneumonia and which exhibited at onset coma and glycosuria without ketosis. The urine sugar became negative the following day, but the signs of meningitis persisted. At autopsy there was a purulent leptomeningitis and also a purulent exudate over the right pleura. Culture from the blood, pleura and meninges showed streptococcus and *Staphylococcus aureus.*

Glycosuria in meningococcic meningitis has been reported in four cases by Cole,[7] in three cases by Box and Nicholson,[8] and in one case each by Bruce and Flexner,[9] Ward and Driver,[10] Hunter [11] and MacNally.[12] Cole [7] observed four cases of coma with glycosuria and ketosis in a series of 20 cases of meningococcal meningitis. Two of the patients were previously known to have suffered from diabetes. In one of these Cole thought that a diabetic coma had been precipitated by the infection. In the second, treatment was instituted for diabetic coma before the existence of meningitis had been suspected. In Cole's other two cases glycosuria and ketosis occurred as a transient phenomenon at the onset of the meningitis and had entirely disappeared in four days. Each patient had a normal sugar tolerance test after the meningitis had been cured. The patients of Box and Nicholson [8] were children, two of whom had transient glycosuria during the first three days of a fatal meningitis. In the other, sugar appeared in the urine during a fatal relapse with hydrocephalus. In the single case reported by Ward and Driver [10] the patient was seen initially in coma with only minimal signs of meningeal irritation, but with glycosuria and ketosis. A diagnosis of diabetic coma was made and during the first 5 hours 110 units of insulin and 1,500 c.c. of 2.5 per cent glucose in saline were given. Three hours after the last insulin had been given the blood sugar was 190 mg. per cent. He rapidly recovered consciousness and then for the first time was recognized

to have signs of meningitis. This was confirmed by lumbar puncture and treated by sulfapyridine with complete recovery. A glucose tolerance test performed prior to his discharge from the hospital showed a normal curve with no glycosuria. Hunter's case presented a similar story of coma accompanied by acetone breath and by sugar and acetone in the urine. Insulin was administered and the urine was thereafter free of sugar and ketones. It was after the treatment of supposed diabetes was complete that signs of meningeal involvement were first recognized. Treatment of the infection with sulfapyridine led to complete recovery. Sugar tolerance after discharge from the hospital was normal and there were no residual signs of diabetes.

Our cases and those in the literature fall into two categories: (1) diabetics in whom meningitis appeared as an incident (cases 1 and 2 of Cole's series and our case 15), and (2) previously healthy individuals in whom glycosuria appeared as a transient phenomenon at the onset of meningitis. In the first group marked glycosuria and ketosis were to be expected since it is well known that infection in diabetes may exaggerate glycosuria and ketosis or precipitate coma.[13, 14] In the other group the situation is not so clear. It appears unlikely that all of those who had sugar in the urine were prediabetic because their number is so much greater than would be expected from the known incidence of diabetes. Moreover transient glycosuria, hyperglycemia and diminished sugar tolerance have been demonstrated in the course of many acute infections,[15] and it seems not unlikely that the high incidence of glycosuria at the onset of meningitis may be only an exaggerated response to a sudden infection of great severity. The accumulated data furnish no evidence to support any one of the various theories for glycosuria in infections such as depression in insular function,[15] inhibition of the action of insulin,[16, 17, 18] or excessive hepatic glycogenolysis.[19, 20, 21] It is also possible, as has been suggested frequently in the literature[4, 6, 10] that the glycosuria is in part attributable to increased intracranial pressure or actual involvement of nerve structures about the fourth ventricle and is similar in mechanism to the piqûre diabetes of Claude Bernard. Perhaps pertinent is the incidence of cranial nerve paralyses in cases of meningitis which have exhibited glycosuria. In the cases of Taylor and McKinstry,[6] Roussel,[5] Ward and Driver,[10] McNally [12] and Cole [7] nerve defects ranging from lateral rectus palsies to complete hemipareses were reported. Among our 16 cases there were at least three definite nerve paralyses. It should be noted, however, in our case 10 and in the reports of Ward and Driver [10] and Hunter [11] glycosuria and ketosis appeared early in the infection before there was any clinical evidence of meningeal involvement. Our data offer no evidence upon such possible mechanisms as depression of insular function.

The fact that glycosuria disappeared promptly following the administration of insulin in some of the cases cannot be used as evidence for or against insulin resistance as a cause since similar prompt recoveries of normal carbohydrate relationships occurred in several cases to which no insulin was given.

From a practical standpoint the most important aspect of glycosuria in meningitis is the possibility that the occurrence of coma with glycosuria, hyperglycemia, and ketosis at the onset of the infection may lead to a diagnosis of diabetic acidosis and that in the meantime the signs of meningitis may be masked or missed entirely. In the cases reported by Ward and Driver [10] and by Hunter [11] glycosuria and other signs indicating disturbed carbohydrate relationships preceded the signs of meningitis and in our case 10 were evident before the spinal fluid had become abnormal. In Cole's second fatal case the initial coma with glycosuria, hyperglycemia and ketosis was diagnosed and managed as diabetic coma for 24 hours before the meningitis was recognized or given the benefit of sulfonamide drugs.

Summary

1. Spontaneous glycosuria occurs frequently at the onset of meningitis. It appeared in 16 of 72 consecutive cases of meningitis and in over one third of 26 cases of meningococcic meningitis.

2. It was encountered in meningitis caused by the meningococcus, the pneumococcus, the staphylococcus, the tubercle bacillus and in one case in which the causative organism was not isolated.

3. Glycosuria was accompanied in many instances by ketosis, hyperglycemia and diminished tolerance to sugar.

4. Glycosuria was transient, disappeared in all cases and persisted beyond the third day in only three of the 16 cases.

5. Coma with glycosuria and ketosis at the onset of meningitis may mask the signs of meningeal involvement, lead to a diagnosis of diabetic acidosis and cause serious or fatal delay in instituting appropriate treatment for the meningitis.

BIBLIOGRAPHY

1. Loeb, M.: Ein Erklärungsversuch der verschiedenartigen Temperaturverhältnisse bei der tuberculösen Basilarmeningitis, Deutsch. Arch. f. klin. Med., 1884, xxxiv, 443.
2. Frew, R. S., and Garrod, A. E.: Glycosuria in tuberculous meningitis, Lancet, 1913, i, 15.
3. Nohecourt, P.: Syndrome de vomissements avec acetonurie au debut des meningites a meningocoques et des meningites tuberculeuses, Prog. Med., 1933, i, 110.
4. Krafchik, L. L., and Slobody, L. B.: Tuberculous meningitis resembling diabetic coma, Arch. Pediat., 1938, lv, 288.
5. Roussel, A. E.: Pneumococcus meningitis simulating diabetic coma with recovery, Atlantic Med. Jr., 1926, xxx, 159.
6. Taylor, F. E., and McKinstry, W. H.: A case of suppurative meningitis with glycosuria simulating diabetic coma, Lancet, 1917, i, 182.
7. Cole, L.: Diagnosis of coma in cerebrospinal fever with diabetes, Lancet, 1942, ii, 421.
8. Box, C. R., and Nicholson, T. G.: The glycosuria associated with meningitis, Lancet, 1917, i, 239.
9. Bruce, J. W., and Flexner, M.: Meningococcus meningitis: report of an unusual case, Arch. Pediat., 1926, xliii, 473.
10. Ward, C. W., and Driver, A. A.: Meningococcal meningitis starting as diabetic coma, Lancet, 1940, ii, 228.

11. HUNTER, R. R.: Glycosuria in meningococcal meningitis, Lancet, 1940, ii, 604.
12. MCNALLY, W. D.: Meningitis with a diabetic coma, Illinois Med. Jr., 1941, lxxx, 507.
13. GREENE, J. A., and KEOHEN, G. F.: Insulin resistance due to infection in diabetes mellitus in man, Jr. Am. Med. Assoc., 1943, cxxi, 173.
14. GREENE, J. A., DAVID, A., and JOHNSTON, G.: Production of insulin resistance in depancreatized dogs, Am. Jr. Physiol., 1942, cxxxvi, 595.
15. WILLIAMS, J. L., and DICK, G. F.: Decreased dextrose tolerance in acute infectious diseases, Arch. Int. Med., 1932, l, 801.
16. SWEENEY, J. S., and LACKEY, R. W.: The effect of toxemia on tolerance for dextrose, Arch. Int. Med., 1928, xli, 257.
17. SWEENEY, J. S., BARSHOP, N., and LEBELLO, L. C.: Effect of toxemia on tolerance for dextrose and on the action of insulin, Arch. Int. Med., 1934, liii, 689.
18. SWEENEY, J. S., BARSHOP, N., LEBELLO, L. C., and ROSENTHAL, R. S.: Effect of toxemia on the tolerance for dextrose and on the action of insulin, Arch. Int. Med., 1934, liv, 381.
19. SOSKIN, S., ALLWEISS, M. D., and MIRSKY, I. A.: Interpretation of abnormal dextrose tolerance curves occurring in toxemia in terms of liver function, Arch. Int. Med., 1935, lvi, 927.
20. SOSKIN, S., and MIRSKY, I. A.: The influence of progressive toxemic liver damage upon the dextrose tolerance curve, Am. Jr. Physiol., 1935, cxii, 649.
21. MIRSKY, I. A.: The etiology of diabetic acidosis, Jr. Am. Med. Assoc., 1942, cxviii, 690.

THE WATERHOUSE–FRIDERICHSEN SYNDROME: OBERVATIONS ON ASSOCIATED ADRENAL INSUFFICIENCY AND REPORT OF FOUR CASES *

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Introduction

With the recent increase in prevalence of meningococcal meningitis, there has been, as might be anticipated, an associated rise in the number of cases of the so-called Waterhouse-Friderichsen syndrome.[1, 2] This condition, characterized by shock, purpura and hemorrhages into the adrenal glands, is encountered in overwhelming sepsis resulting as a rule from meningococcus infection, but it may also be due to any one of a variety of organisms.[3, 4, 5] Because this symptom complex has been described infrequently in the past, it becomes of interest to review this disorder with particular emphasis on possible relationships of adrenal insufficiency to the underlying mechanisms of the syndrome. In the past eight months, four adult patients with the Waterhouse-Friderichsen syndrome were admitted to the Presbyterian Hospital. In two of these, detailed studies pertaining to abnormalities of electrolytes, sugar, and non-protein nitrogen in the blood were carried out. In addition, the possible therapeutic value of various adrenal cortical substances and fluids was observed. The data obtained and the results of such therapy are presented in this report.

Disease Picture

A review of the literature, with slightly more than 100 cases recorded, indicates that the Waterhouse-Friderichsen syndrome is more common in children, the majority of patients being less than two years of age, 90 per cent occurring in children under 10 years, and both sexes being equally affected.[3, 4, 5] The onset is characteristically rapid, often with prodromal malaise, chills, fever, and joint pains. In a matter of a few hours, signs of marked prostration appear, petechiae and purpura become evident, and areas of blotchy cyanosis are seen. The patient becomes rapidly stuporous or comatose, with progressive peripheral circulatory collapse, and death usually occurs within 12 to 36 hours after onset.

Physical examination usually shows a desperately ill patient, with variable but often high fever, weak or imperceptible pulse, and blood pressure too low to be determined. An extensive purpuric rash appears, and conjunctival hemorrhages may result in the unusual manifestation of "bloody

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tears." Profound and variable cyanosis is usually present. Clinical evidence of meningeal irritation is either minimal or absent, probably because the rapid fulminating course does not allow time for extensive meningeal infection to take place. Pains in the extremities and joints may cause great distress.

Detailed laboratory studies are infrequently recorded, because of the rapid course of the disease process. Data are available to indicate that, in cases resulting from meningococcemia, a mild to moderate polymorphonuclear leukocytosis is the rule, with a tendency to thrombocytopenia. Despite the purpuric and thrombocytopenic tendency, tests of capillary fragility have not been reported. In a few cases, there has been found an elevated nonprotein nitrogen and a lowered blood sugar.[4, 5, 6, 7] The spinal fluid is characteristically normal, and culture of the spinal fluid is usually negative. Blood cultures are usually positive.

TABLE I

Chemical Changes in the Blood in Two Cases of the Waterhouse-Friderichsen Syndrome

Name	Urea Nitrogen	Sugar	Sodium	Protein	Chlorides	CO_2
	mg. per 100 c.c.	mg. per 100 c.c.	m. eq. per l.	Grams per 100 c.c.	m. eq. per l.	m. eq. per l.
S. M. Case 1	58	50	127.9 122.9	6.2	95.4	17.5
J. B. Case 2	26	245	128.6	7.2	100	18.6

At autopsy, the principal findings are the invariable hemorrhages into the adrenal glands, and frequently into the skin, muscles, brain and other organs. Focal myocarditis, focal necroses of the liver, and acute splenic tumor are often present.

An accurate antemortem diagnosis is difficult and infrequent. The syndrome may readily be confused with the onset of many infectious processes. In many instances, the picture is not unlike that produced by a blood dyscrasia, such as acute leukemia or a crisis in thrombocytopenic purpura. Acute rheumatic fever may be suggested by the joint complaints. Other cases resemble acute poisoning or heart failure, by virtue of the cyanosis, collapse, and respiratory difficulty. The comatose condition may be confused with cerebral accidents or uremia. The skin rash needs to be distinguished from that of the rickettsial diseases.

CASE REPORTS

Case 1. S. M., a 32 year old white American housewife, was in perfect health until 30 hours before admission, when she was awakened during the night by a shaking chill lasting one hour. Temperature was subsequently found to be 105° F. by mouth, and after several hours she complained of generalized aches most marked in the extremities. A skin eruption was then observed on her arms and legs. A

physician was called, and administered antipyretics with subsequent drop in temperature to normal. Because of increasing prostration, more severe aches and spreading skin lesions, hospital admission was advised.

On admission, the patient appeared acutely ill and cyanotic with a rectal temperature of 98° F. She was pulseless, and the blood pressure could not be obtained. Her heart rate was 140. A purpuric rash varying from petechial hemorrhages to large ecchymotic areas was scattered over the entire body. Bilateral conjunctival hemorrhages were present. There were no signs of meningeal irritation, and the remainder of the examination showed no abnormalities.

Laboratory tests: The blood showed 14 grams of hemoglobin, the red cell count 3,870,000, leukocytes 17,000 with 56 per cent polymorphonuclears and a marked shift to the left. Platelets were 32,000. The capillary resistance, as measured by the negative pressure suction pump, was normal on admission: no petechiae were observed with a pressure of minus 30 mm. of mercury exerted for one minute. Thirty hours later, petechiae were observed at a pressure of minus 20 mm. of mercury for one minute. The hematocrit was 48.6 per cent, and the sedimentation rate was 25 mm. in one hour. Urinalysis showed a three plus albuminuria, and occasional red and white blood cells. Lumbar puncture produced crystal clear fluid with a pressure of 170 mm. of water, containing 2 cells per cu. mm., protein 63 mg. per cent, sugar 64 mg. per cent, and culture gave no growth. The serum proteins were 6.2 grams per cent, the serum CO_2 17.5 milli-equivalents per liter, serum chlorides 95.4 milli-equivalents per liter, the serum sodium 127.9 milli-equivalents per liter on one occasion and 122.9 milli-equivalents per liter on another determination, urea nitrogen 58 mg. per cent, serum sugar 50 mg. per cent.

Course: On admission, the diagnosis of meningococcemia with the Waterhouse-Friderichsen syndrome was suspected. Throughout her course, the temperature varied from 97.4 to 99.4° F. by rectum. The admission blood culture was subsequently found to contain meningococci. On admission, she was immediately given an infusion of 2,000 c.c. of 5 per cent glucose in saline, containing five grams of sodium sulfadiazine. She also received a blood transfusion of 500 c.c. Six hours later, a blood pressure of 60 mm. Hg systolic and 40 mm. diastolic was obtained, and the radial pulse became palpable. In the course of the next three days, she received a total of 20 milligrams of desoxycorticosterone acetate,* 140 c.c. of Upjohn's cortical extract, 50 c.c. of eschatin, and further saline and glucose infusions. During this period, blood pressure varied from 70 mm. Hg systolic and 40 mm. diastolic to 110 mm. systolic and 74 mm. diastolic, and the patient became somewhat more alert. Further parenteral sodium sulfadiazine maintained the daily blood levels between 16 and 18 mg. per cent. With no new significant findings, death occurred suddenly 72 hours after admission.

Autopsy showed the hemorrhagic skin and mucous membrane lesions noted clinically. In addition, there was an acute fibrinous pericarditis and acute focal myocarditis. The adrenal glands were of normal size, but 80 to 90 per cent of the glands were grossly hemorrhagic, and histologically almost the entire cellular structure of both cortex and medulla was obliterated by extravasated red blood cells. No examination of the central nervous system was permitted.

Case 2. J. B., a 16 year old white schoolboy, who gave a history of a mild upper respiratory infection for the preceding week, suddenly felt ill 10 hours before admission. He developed a shaking chill and fever to 105° F., and eight hours later was found comatose at home. His physician was summoned, who found his temperature to be 109° F. (?). He was then transported by ambulance to the Presbyterian Hospital.

* Supplied through the courtesy of Roche-Organon, Inc., Nutley, New Jersey.

On admission, the patient appeared acutely ill, cyanotic, and comatose. Rectal temperature was 106° F., pulse was 130 weak, respirations 30, and blood pressure was 80 mm. Hg systolic and 55 mm. diastolic. A generalized petechial eruption with scattered areas of purpura was present. There were hemorrhagic tears. There was generalized rigidity, neck flexion was somewhat resistant, and the Kernig test was positive. The remainder of the examination was normal.

Laboratory tests: The blood showed 14.3 grams of hemoglobin, the red cell count 5,200,000, the leukocytes 12,000 with 90 per cent polymorphonuclears and a marked shift to the left on admission (later rising to 32,000). The platelets were 121,000. The sedimentation rate was 13 mm. in one hour. No urine was obtained. Lumbar puncture produced crystal clear fluid with a pressure of 128 mm. of water, containing 8 cells per cu. mm., protein 23 mg. per cent, sugar 120 mg. per cent, and culture was negative. The serum urea nitrogen was 26 mg. per cent, serum sugar 245 mg. per cent, serum proteins 7.2 grams per cent, serum CO_2 18.6 milli-equivalents per liter, serum chlorides 100 milli-equivalents per liter, serum sodium 128.6 milli-equivalents per liter. The blood culture taken on admission was positive for meningococci, but nose and throat cultures were negative.

Course: On admission, it was felt that the patient had a sepsis, associated with a possible Waterhouse-Friderichsen syndrome. He was promptly given 2000 c.c. of intravenous saline and glucose containing seven grams of sodium sulfadiazine, a whole blood transfusion of 500 c.c., and 50 c.c. of eschatin. Despite the above, however, his temperature remained elevated, and he grew steadily worse. He became cyanotic with irregular respirations, developed a progressively weaker pulse, and blood pressure dropped to 70 mm. Hg systolic and 20 mm. diastolic. The patient died 29 hours after the onset of his disease.

Autopsy revealed the petechial and hemorrhagic lesions widespread throughout skin, muscles and mucous membranes. There were focal necroses of the liver. The meninges and the brain were normal. The adrenals were grossly normal, but microscopically showed extensive edema and hemorrhage of the capsule. There were only a small number of hemorrhagic extravasations into the cortical tissue. The medulla of the glands was normal, save for a moderate polymorphonuclear infiltration.

Case 3. E. A., a 71 year old housewife, was known to have had a mild hypertension for 15 years, but was in good health until 20 hours before admission. When awakened from her usual noonday rest, she was confused and complained of weakness in her left arm and leg. Her physician was summoned, and on his arrival within an hour found her to be comatose, and her oral temperature 105° F. He considered the patient to have had a cerebral accident, and administered antipyretics without avail. During that evening her temperature rose to 106° F., generalized purpura appeared, and she was brought to the hospital by ambulance.

On admission, the patient was obviously in extremis, comatose, and cyanotic. Respirations were gasping and irregular. Generalized purpura was present. Temperature was not taken; blood pressure was 55 mm. Hg systolic and 50 mm. diastolic; pulse was imperceptible. The heart rate was 120. The pupils were fixed, but the neck was supple. The remainder of the examination was not remarkable.

The patient was felt to have had a cerebral accident. Because of her cyanosis, she was placed in oxygen, but died one-half hour after admission.

At autopsy, the generalized hemorrhages as noted clinically were prominent. There was an acute interstitial myocarditis. The adrenal glands were of normal size, but signs of gross hemorrhage extended throughout each gland. Histological examination revealed that widespread red blood cell extravasations obscured the architecture of most of the cortex. Those cortical cells in the portion of the gland with normal architecture showed no evidence of toxic necrosis. The brain and meninges showed no signs of recent vascular thrombosis, hemorrhage, or inflammation.

Case 4. S. S., a 47 year old housewife, was perfectly well until 24 hours before admission, when she complained of malaise and found her temperature to be 102° F. by mouth. The physician who attended her made a diagnosis of "grippe." Twelve hours later during the evening, she noted a rash appearing over her entire body, and experienced some difficulty in breathing. She complained bitterly of pains in her arms and legs, and said that they felt paralyzed. Five hours before admission, she began having greater respiratory difficulty, and her husband noted that she was becoming blue. Her temperature was 104° F. by mouth. She was given oxygen for several hours at home, and then was transported by ambulance to the Presbyterian Hospital.

On admission, she was comatose, cyanotic, and extremely dyspneic. Petechiae were scattered sparsely over the buccal membranes and the extremities. The conjunctivae were hemorrhagic, and there were "bloody tears." Pulse was imperceptible; the heart rate was rapid. Despite oxygen and stimulants, she died five minutes after admission. Blood cultures, as well as those of nose and throat, were later reported as positive for meningococci.

Autopsy revealed the generalized hemorrhages of the skin, subcutaneous tissues, muscles, heart, intestines, and especially of the adrenal glands. The adrenals were of normal size and shape. The whole substance of the gland was grossly hemorrhagic. Histologically, the usual architecture was replaced by massive extravasations of red blood cells. The brain and meninges were normal.

Discussion

The Waterhouse-Friderichsen syndrome has been reviewed on previous occasions.[3, 4, 5, 7, 8, 9] But with 806 cases of meningococcus meningitis reported in New York City during the first five months of 1943 as compared to 48 cases in a similar period in 1941, it is fair to expect that an increase in the Waterhouse-Friderichsen cases will occur. This is suggested by the admission of four patients with this disorder, described as being much more common in childhood, to the adult wards of Presbyterian Hospital during the eight-month period ending April 1943. As diagnosis is difficult and therapy of little avail unless the initial sepsis can be rapidly overcome, the early recognition of this disease assumes increasing importance.

The question has often been raised as to the rôle of the adrenal glands in the production of this syndrome. Adrenal cortical insufficiency is suggested by: (1) the clinical pattern of hypotension, dehydration, and vomiting; (2) the laboratory findings of lowered blood sodium in our patients, an elevated non-protein nitrogen occasionally associated with hypoglycemia; and (3) the pathologic finding of hemorrhagic damage to the adrenal glands.

On the other hand, the clinical picture described above, although consistent with a diagnosis of hypoadrenalism, is not specific for this condition, and may be the result of overwhelming infection with generalized tissue damage. Furthermore, as brought out by the autopsy findings in the second case reported in this paper, the extent of adrenal cortical destruction may be small in the Waterhouse-Friderichsen syndrome; and it is well known that only a small portion of the adrenal cortex need remain for the preservation of normal function in the experimental animal. Although there are a

small number of patients seen in an Addisonian crisis who fail to respond to specific treatment, the majority of patients react favorably to the administration of fluids, electrolytes, and adrenal cortical replacement therapy.[10] The lack of response in the first two cases reported here may be an added argument that hypoadrenalism is not the primary cause of death, but is conceivably a contributing factor.

Recent studies indicate an increase in the urinary excretion of hormonal substances, presumably of adrenal origin, in infections as well as in severe burns and postoperative states.[11] For these reasons, the possible rôle of the adrenal glands should not be disregarded, since in the presence of severe infection, varying degrees of hypoadrenalism, if untreated, may be sufficient to precipitate a fatal outcome. It may be that if adequate supportive adrenal therapy is administered, such therapy may successfully bolster a seriously embarrassed body economy. This replacement therapy should be conducted along such lines as suggested by Loeb in the discussion of the therapy of an Addisonian crisis.[10, 12] Recently there have been reported three cases which were clinically the Waterhouse-Friderichsen syndrome, and which recovered following active treatment along the general program of combating both the septicemia and the possible adrenal disturbance.[13, 14, 15]

Acute and overwhelming septicemia initiates the disease resulting in the Waterhouse-Friderichsen syndrome, and therefore constitutes the first therapeutic consideration.[16] Rapid and adequate chemotherapy is the accepted means of combating the blood stream infection. Sulfadiazine is generally considered to be the most effective and least toxic sulfonamide in these cases, and it should be administered by intravenous and subcutaneous methods as well as the usual oral route. Adequate and possibly high sulfadiazine blood levels should be maintained in the presence of such a severe process. Unless the infection is overcome, even the most successful therapy of the possible adrenal insufficiency would be of no avail.

Inasmuch as many of the organisms responsible for this syndrome are known to be highly susceptible to the antibacterial action of penicillin,[17, 18] and as this agent exerts its effect against the offending organisms without the usual lag phase observed with the sulfonamides,[19] it is possible that penicillin or related substances may prove to be even more potent therapeutic weapons in combating this type of sepsis.

Summary

1. Four cases of the Waterhouse-Friderichsen syndrome in adults are reported.

2. In two patients in whom analyses were made, a decrease in the serum sodium and an increase in the non-protein nitrogen compatible with adrenal-cortical insufficiency were encountered.

3. These changes bore no relationship to the extent of damage observed in the adrenal cortex at autopsy.

4. The rôle of hypoadrenalism in the mechanism of this syndrome is not as yet established.

5. Therapy should be directed primarily towards the treatment of sepsis, and secondarily towards the correction of possible associated adrenal cortical insufficiency.

BIBLIOGRAPHY

1. Waterhouse, R.: A case of suprarenal apoplexy, Lancet, 1911, i, 576.
2. Friderichsen, C.: Nebennierenapoplexie bei kleinen Kindern, Jahrb. f. Kinderh., 1918, lxxxvii, 109.
3. Aegerter, E. E.: The Waterhouse-Friderichsen syndrome; a review of the literature and a report of two cases, Jr. Am. Med. Assoc., 1936, cvi, 1715.
4. Kunstader, R.: The Waterhouse-Friderichsen syndrome, Arch. Pediat., 1939, lvi, 489.
5. Sacks, M.: Fulminating septicemia associated with purpura and bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome); report of 2 cases with review of the literature, Ann. Int. Med., 1937, x, 1105.
6. Magnusson, J. H.: Contribution to the knowledge of acute suprarenal insufficiency in children, Acta paediat., 1934, xv, 396.
7. Lindsay, J. W., Rice, E. C., Selinger, M. A., and Robin L.: The Waterhouse-Friderichsen syndrome, Am. Jr. Med. Sci., 1941, cci, 263.
8. Monfort, J. A., and Mehrling, J. H.: The Waterhouse-Friderichsen syndrome, Am. Jr. Dis. Child., 1941, lxii, 144.
9. Michael, P., and Jacobus, L.: The Waterhouse-Friderichsen syndrome, Arch. Pediat., 1942, lix, 141.
10. Loeb, R. F.: The adrenal cortex and electrolyte balance, Bull. New York Acad. Med., 1942, xviii, 263.
11. Weil, P., and Brown, J.: A cortin-like action of extracts of human urine, Am. Jr. Physiol., 1939, cxxvi, 652.
12. Loeb, R. F.: Diseases of the adrenals, 1943, Oxford University Press, New York, p. 783.
13. Grace, W. A., Harrison, C. V., and Davie, T. B.: Suprarenal hemorrhage in meningococcal septicemia, Lancet, 1940, ii, 102.
14. Carey, T. N.: Adrenal hemorrhage with purpura and septicemia (Waterhouse-Friderichsen syndrome) with recovery; case report, Ann. Int. Med., 1940, xiii, 1740.
15. Ruchs, W., and Hobson, J.: Purpura fulminans (Waterhouse-Friderichsen syndrome), Jr. Pediat., 1943, xxii, 226.
16. Finland, M., and Dingle, J.: Diagnosis, treatment and prevention of meningococcic meningitis, War Med., 1942, ii, 1.
17. Chain, E., Florey, H. W., Gardener, A. D., Heatley, N. G., Jennings, M. A., Orr-Ewing, J., and Sanders, A. G.: Penicillin as a chemotherapeutic agent, Lancet, 1940, ii, 226.
18. Herrell, W. E.: Further observations on the clinical use of penicillin, Proc. Staff Meet. Mayo Clin., 1943, xviii, 65.
19. Hobby, G. L., Meyer, K., and Chaffee, E.: Mechanism of action of penicillin, Proc. Soc. Exper. Biol. and Med., 1942, l, 281.

MENINGOCOCCIC MENINGITIS—SULFADIAZINE THERAPY (REVIEW OF TWENTY CASES) * †

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Introduction

An increased occurrence of all types of contagious diseases may be anticipated incidental to the mobilization of large groups of men. During the year 1941, no cases of epidemic meningitis were seen in this institution, whereas from June 1942 through June 1943, 20 cases of this disease were treated here (Station Hospital, Fort Totten, New York). These cases were sporadic throughout the metropolitan area. Their scatter precluded epidemic consideration. No direct contact had been established between any two of this group of patients. Routine pharyngeal cultures of the men comprising the groups from which these cases had been isolated disclosed but five carriers. In none of these was the recovered meningococcus similar in type to that found in the men with active disease.

Favorable reports abound in the literature concerning the use of sulfanilamide and its derivatives, in the treatment of meningococcic meningitis.[1, 2, 3, 4, 5, 6] Sulfadiazine and its soluble sodium salt was the only sulfonamide utilized in the management of the 20 consecutive cases reported here. In one of our earliest cases, polyvalent anti-meningococcic serum was administered intravenously in conjunction with chemotherapy. Such a severe reaction ensued that we abandoned the use of serum thereafter. The plan of treatment conformed in general to that outlined in S.G.O. Circular Letter No. 17.[7]

Clinical Features

The prodromal period in the majority of patients was brief, rarely exceeding two to three days, and was characterized in the main by mild sore throat, chills and fever, headache, nausea and vomiting. In two instances, the patients were found unconscious in bed, with no history of preceding illness or disability.

Headache, present in practically all cases, was a most distressing complaint. It was generally described as throbbing or pounding, and diffuse in character. This symptom, difficult to relieve, practically paralleled the clinical response of the patient—as the latter improved, the former lessened. Nausea and vomiting were frequent concomitants of this symptom. Nuchal rigidity of varying grades of severity, found in nearly all cases, lasted on an average from four to five days.

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† The authors wish to express their appreciation to Colonel A. J. Vadala, M. C., for his kind assistance in the preparation of this paper.

In slightly more than half, the classical, full-blown picture of meningitis (marked nuchal rigidity, stupor or active delirium, positive Kernig sign, absent abdominal reflexes, etc.) presented itself. The remainder, although not so severe, offered no difficulties in diagnosis.

Various levels of depression, ranging from mild somnolence to lethargy, usually accompanied by motor restlessness, were fairly common. Ocular signs, strabismus, nystagmus, oculogyric movements, were noted in three cases.

Cutaneous lesions, seen in 11 patients, were principally petechial in nature, located predominantly over the anterior abdomen and extremities. Two patients manifested purpuric eruptions. One had varying sized coalescent, well demarcated areas of hemorrhage over the forehead, body, and extremities. Massive hemorrhagic extravasations occurred in both lower extremities up to the knees. Reactive edema caused the facies to assume a bloated appearance, and the legs to enlarge twice their normal size. The involved skin areas became anesthetic, underwent a dry necrosis, and formed hard, black eschars. This patient exhibited the clinical picture of the so-called Waterhouse-Friderichsen syndrome, and survived his illness.

Laboratory Studies

A polynucleosis of the peripheral blood was a universal finding. The total white blood cell counts ranged from 16,300 to 39,800.

The gross appearance of samples of cerebrospinal fluid obtained on initial puncture varied from slight turbidity to cloudiness. Stained smears of the sediment after centrifugation, yielded a gram-negative intracellular diplococcus in 17 (85 per cent) instances. Successful cultures were obtained in 15 (75 per cent) cases.* "It is important to remember that meningococci in spinal fluid undergo solution very readily, a solution which is probably an autolysis with the result that spinal fluid which may be full of polys contains very few recognizable organisms. This readiness to go into solution may cause problems in cultivation." [8]

The relatively large number of successful cultures in this series is, we feel, due to the practice of early spinal puncture, and the ready institution of culturing procedures. These steps will lessen the number of unsuccessful implants.

Blood cultures of venous blood, withdrawn within a few hours or less of admission, were positive in seven (35 per cent) patients. It is of interest to note that five of these were from patients with cutaneous lesions, as could be anticipated.

Immunologically, of the 15 positive recoveries of the meningococcus by culture, 13 and 2 were demonstrated to be of the epidemic strains Type I and Type II, respectively.*

* Second Service Command Army Laboratories.

Management

Diagnostic tap was done on all suspected cases upon admission. Unless some indication warranted it, e.g. signs of block, failure to respond to therapy, etc., this procedure was not repeated. Blood for culture was obtained from all at the same time.

As soon as the diagnosis was verified, an initial dose of 5 grams of sodium sulfadiazine in 100 c.c. of distilled water was administered intravenously; this latter, even though the patient could take the drug orally. Subsequent doses of 2 grams were then given regularly every four hours for the next 24 hours, either orally or intravenously, as determined by the patient's ability to ingest or retain the medication. The oral route was substituted in all those receiving intravenous therapy as soon as the clinical condition permitted. One gram doses every four hours until the temperature returned to normal, and from this point on four times daily for the next seven days, was the course then pursued.

During the acute phase of the disease, blood sulfa levels were determined daily, and upon amelioration, every other day. Complete blood counts and urinalyses were done routinely every other day so long as chemotherapy was employed.

It was the general policy not to administer parenteral fluids unless necessary. This group of young and robust males was not affected adversely by slight or moderate degrees of dehydration. So long as a urinary output of 750 c.c. or more was obtained during the first 24 hours, no parenteral fluids were employed. It was found that an adequate urinary excretion could be attained by fluids taken orally if frequently administered. In but three patients was it necessary to resort to the use of intravenous fluids for short intervals because of vomiting.

The sedation of delirious and restless patients was fairly well maintained by the intramuscular injection of paraldehyde in quantities of 5 to 10 c.c. This dose could, upon necessity, be safely repeated within several hours. On a few occasions the drug was administered intravenously with good results. "This drug possesses a wide margin of safety. Very large doses cause only prolonged unconsciousness, fatalities being quite rare." [9]

The sudden development of hypotension, feeble pulse, marked asthenia, and semi-stupor, marked the clinical deterioration of one patient (case 17). The blood pressure dropped to 70 mm. of Hg systolic and 40 mm. diastolic (mercurial manometer). Aqueous adrenal cortical extract was given intramuscularly in conjunction with physiologic saline solution intravenously. The blood pressure slowly rose to 110 mm. systolic, 50 mm. diastolic; 114 mm. systolic, 52 mm. diastolic; and 112 mm. systolic, 60 mm. diastolic. By the third day, clinical improvement was definite and progressive. All in all, 65 c.c. of extract were given.

Marked bladder atony necessitated the use of an indwelling catheter for a period of seven days before spontaneous urination was resumed in this patient.

TABLE I

Summary of 20 Cases

Case No.	Age	Spinal Fluid				Drug		Lab. Data							Clinical Course							
		Turbidity	Smear	Culture, Gr.	Punctures, No.	Quantity, Gr.	Blood Level	Duration, Days	Reactions	Bl. Cult. Gr.	W.B.C.	Urine	Serology	Pharyn. Cult.	Temp. High	Temp. Days	Hosp. Days No.	Severity	Complication	Sequelae	Disposition
1	22	++	+	I	1	66	15	12		–	17,100	–	–	–	102	2	24	+++		none	duty
2	28	+	—	–	1	83	10	10		–	16,300	–	–	–	101	2	20	+		none	duty
3	34	+++	+	–	3a	45	13.1	5		–	29,350	–	–	–	103	6	66	+++	+d	none	duty
4	33	+	+	II	1	50	8.4	8		–	29,800	–	–	–	102.2	1	23	++		none	duty
5	19	++	+	–	1	39		7		–	21,250	–	–	–	105	3	28	++		none	duty
6	26	++	+	I	1	5		(fulminating case—died within 12 hours)													death
7	20	+++	+	I	2	40*	25.7	4		I	24,500	rbc	–		103.4	4	4	++++	+e		autopsy
8	21	++	+	I	3	41	10.2	6		–	37,250	–	–	–	101.8	2	7	++++	+f	none	duty
9	19	+	+	I	1	62	9.1	9		–	27,400	rbc	–	–	104	3	23	++		none	duty
10	32	++	+	I	2	46	21	13		I	28,400	rbc	–	–	104	5	17	++		none	duty
11	23	+	+	–	1	46	7	8		–	21,600	–	–	–	103.5	2	12	++		none	duty
12	39	+	–	I	1	80	21	13		I	32,500	–	–	–	103	3	19	++		none	duty
13	31	+++	+	–	2	53	17	9		–	32,600	–	–	–	103.6	3	21	++++		none	duty
14	24	++	+	I	1	40	3	10		–	22,750	rbc	–	–	100.6	3	13	+		none	duty
15	31	+	+	I	1	40	5	8	+b	–	18,700	–	–	–	101.2	1	12	+		none	duty
16	26	+	+	I	1	59	14	10	+c	I	39,800	–	–	–	104	3	25	+++		none	duty
17e	22	+++	+	I	1	86	8	13		I	18,700	rbc	–	–	104	17	90	++++	+g, h		
18	25	+++	+	II	1	75	17	10		II	25,500	rbc	–	–	105.8	4	28	+++	+i, j	none	duty
19	28	++	+	I	1	50	6	9		–	20,100	rbc	–	–	102.5	2	30	++		none	duty
20	22	–	–	–	1	–	–	–		I	32,000	–	–	–	103.4	1	18	+		none	duty

* Serum administered and discontinued.
a Suspected block—one cisternal tap done.
b Nausea and vomiting (late in disease).
c Rash and fever.
d Motor aphasia.
e Waterhouse-Friderichsen syndrome.
f Left facial and abducens paresis.
g Patient still in hospital.
h Areas of cutaneous gangrene.
i Pyarthrosis—right knee.
j Radiculitis—right S_{1-5}.

Of unusual interest is case 20. This patient was hospitalized because of chills, fever, petechial rash, generalized aches and pains. The cerebrospinal fluid contained 80 cells per cu. mm. No organisms were seen on smear or recovered by culture of this fluid. All symptoms cleared up within 24 hours without chemotherapy. Blood obtained for culture on admission was later reported as positive for meningococci. This was manifestly a case of spontaneous recovery in a patient with acute meningococcemia and early cerebral irritation.

Complications, Fatalities

Drug reactions were encountered in three patients. Jargon aphasia and motor perseveration in one, nausea and vomiting, rash and fever in two were the clinical manifestations of these reactions. Fortunately, these occurred rather late in the course of the disease, when withdrawal of the drug did not deleteriously affect the progress of the patient.

No renal complications were evidenced in this group. Microscopic hematuria was demonstrated in the admission specimens of urine obtained from seven patients. This cleared up, however, under therapy.

Pyarthrosis of the right knee occurred once. Repeated aspiration, semifixation, and skin traction effected a rapid response with no residual joint changes. Culture of the aspirated fluid did not yield the meningococcus. Subsequent radicular pains in the distribution of right S1–S5 may have been due to the traction employed. Gradual relief of this pain was accomplished by physiotherapy.

A left facial and abducens paresis with spontaneous regression and eventual complete cure, was seen in one case.

The apoplectic form of meningococcic cerebrospinal meningitis, or the Waterhouse-Friderichsen syndrome, was diagnosed clinically in one patient. Substitutional therapy, the use of adrenal cortical extract, was in this instance a life saving measure.[11] ?

Two deaths resulted in this series. One occurred within less than 12 hours after the onset of the disease; the other, four days after admission. Autopsy performed on the latter revealed a severe, bilateral, hemorrhagic necrosis of the suprarenals.*

Summary and Conclusions

A review of the salient clinical features in 20 consecutive cases of meningococcic meningitis is herewith reported.

The exhibition of the drug sulfadiazine, according to the plan described, attained adequate blood concentrations, effected satisfactory clinical responses, and resulted in few complications, none of which left permanent residua.

* Detailed report of these cases of the Waterhouse-Friderichsen syndrome to be published.

The so-called Waterhouse-Friderichsen syndrome was encountered in two patients. The survival of one of these with substitutional therapy augurs well for the outlook of this much dreaded complication.

A mortality of 10 per cent was incurred. It is felt that in a larger group of cases this percentage could be even less.

BIBLIOGRAPHY

1. KANTOR, H. I.: Sulfapyridine in meningococcus meningitis: review of the literature and report of a case, New York State Jr. Med., 1940, xl, 1526.
2. MAIER, CONRAD: Specific treatment of epidemic meningitis with sulfanilamide derivatives (Dagenan and "Ciba 3714"), Schweiz. med. Wchnschr., 1940, lxx, 879.
3. DINGLE, J. H., THOMAS, LEWIS and MORTON, A. R.: Treatment of meningococcic meningitis and meningococcemia with sulfadiazine, Jr. Am. Med. Assoc., 1941, cxvi, 2666.
4. GERNEZ, CHARLES and HURIEZ, CLAUDE: Considerations on the sulfamide treatment of the meningococcic cerebrospinal meningitis, La presse med., 1941, xlix, 25.
5. FELDMAN, H. A., SWEET, L. K., and DOWLING, H. F.: Sulfadiazine therapy of purulent meningitis, including its use in twenty-four consecutive patients with meningococcic meningitis, War Med., 1942, ii, 995.
6. HARRIES, G. EMRYS: Cerebrospinal fever. A review of 500 cases treated by chemotherapy without intrathecal serum, Brit. Med. Jr., 1942, ii, 433.
7. S.G.O. Circular Letter No. 17, February 23, 1942, Chemotherapy in infectious diseases and other infections.
8. ZINSSER, HANS: Textbook of bacteriology, 5th edition, 1925.
9. GOODMAN, LOUIS and GILMAN, ALFRED: The pharmacological basis of therapeutics, 1941, Macmillan Company, New York.

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MENINGOCOCCEMIA WITHOUT MENINGITIS; A STUDY MADE AT THE STATION HOSPITAL, FORT GEORGE G. MEADE, MARYLAND *

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MANY contributions have appeared in American and foreign journals describing meningococcemia without meningitis. Most of the reports have been of one to three cases with a discussion of the literature. Because of the wide distribution of such reports, it is not our purpose to summarize these findings but to report our observations on 11 cases which we treated. Sulfadiazine was the drug used in our series and, because of this, we have observed certain differences from the cases seen previous to this form of therapy. The outstanding difference is that our cases would fall into the acute meningococcemia class rather than in the subacute or chronic group, which has been the classification used prior to this.

Excellent discussions of the syndrome, as recent as 1939, are available, and the study of these articles will be sufficient to give one a good idea of the condition as well as a pre-sulfonamide view of the vagaries of the disease. Binns and Fothergill [1] have an excellent review of the literature up to 1931 with a description of the syndrome and a report of one case. Carbonell and Campbell [2] describe three cases and present a description of the disease from a study of 33 cases which they collected from the American literature up to 1938. Applebaum [3] reports a summary of 15 cases of his own, seven of which subsequently developed meningitis. In 1939, Heinle reported five cases.

Since the inauguration of sulfonamide therapy, there have been several individual case reports. In the Australian literature, Moss [5] reports four cases treated with sulfapyridine as well as an excellent discussion of the disease. In the American literature, Watson [6] reported one case treated with sulfanilamide and he also reviews the literature. He states that 12 cases had been reported since the start of sulfonamide therapy without a fatality. Kattwinkel [7] also reported one case treated with sulfanilamide.

The following is the abstract of our case histories in chronological order:

Case 1. G. G. was admitted to the Station Hospital on December 24, 1942, complaining of chill, generalized malaise, aggravation of the symptoms of an upper respiratory tract infection which he had had for the previous two weeks, severe headache and a rash. All the above occurred within 24 to 36 hours of the time he was admitted to the hospital.

Examination revealed that he did not look more ill than other patients with an upper respiratory tract infection. There was a generalized fine petechial eruption

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that was prominent on the extremities. Some lesions were also present on the buccal mucosa but none was seen on the palate. There was no nuchal rigidity, but some pain was present at the base of the neck on extreme flexion and rotation.

His white blood cell count was 28,400 with 31 young and 63 segmented granulocytes. The spinal fluid contained three white cells of which two were granulocytes and one was a lymphocyte.

He was placed on the usual sulfonamide therapy. That afternoon, he complained of pain in both knees and elbows; the right elbow had ten degrees limitation in extension. By December 27, the eruption had almost entirely disappeared but the joint pain and involvement had progressed. At this time his left wrist, metacarpophalangeal joint of the left index finger, right elbow, right wrist, and left knee were definitely swollen and tender. No heart murmurs were heard. The liver and spleen

FIG. 1. Bullous lesions on foot in case of meningococcemia.

were not palpable. A platelet count on December 26 was 152,000. The white cells were 14,350 with 2 young and 79 mature granulocytes. The sulfadiazine was discontinued on the assumption that this patient had rheumatic fever and salicylates were administered.

On December 28, the left knee was normal, but the other joints were still involved. At noon, it was reported that a Group I meningococcus was found in the blood stream and sulfadiazine administration was resumed.

On December 30, the petechial eruption was entirely gone. By that date, all the joints except the right elbow had returned to normal. This joint continued to be swollen though less tender and red. Its motion was still limited. The orthopedic consultant saw him on January 5, 1943 and advised against tapping the joint at that time. The joint gradually became normal in size and by January 11, no abnormality could be made out. With active motion and physiotherapy, the pain and limitation of motion disappeared by February 22. A roentgenogram of the joint was taken on January 14 and showed some roughening of the trochlear notch which had the appearance of an old injury or osteochondritis.

Two electrocardiograms, taken on January 8 and January 28, were normal. The white blood cell count and differential count returned to normal on December 30, the seventh hospital day. The blood sulfadiazine level reached 14.1 mg. per cent at the height of therapy. The temperature reached a normal level on the sixth hospital day.

Case 2. V. E. J. was admitted on February 26 with a history of having felt perfectly well until the night of February 25 when he developed a chill while watching a moving picture. He felt feverish that night but went to his barracks to sleep. He awakened on February 26 with a persistent headache and slight cough. In the Receiving Office of the hospital, a rash was noticed.

Examination showed him to appear mildly ill. On his trunk and extremities, he had pink, dark red, and brown macules of various sizes. His throat was slightly injected. He had some muscle guarding of the neck but no rigidity. He had a questionable bilateral Kernig sign. His temperature was 101.8° F. and rose to 103.6° F. several hours later. Shortly before the rise in temperature he vomited twice. A spinal tap was done shortly after admission. The fluid showed five white cells, two of which were polymorphonuclears. The spinal fluid sugar was 71 mg. per cent and a trace of globulin was present. No organisms were grown on culture. The white blood cell count on admission was 26,000 with 80 per cent polymorphonuclears of which 20 were young forms.

He was seen by the Dermatologic Consultant on February 27, who described the lesions as pink macules with deeper colored centers and suggested that they were of the erythema multiforme variety.

On February 27, a Group I meningococcus was grown from the blood and the patient was placed on sulfadiazine. On February 28, the rash was fading rapidly but those lesions that were still present did not completely fade on pressure.

From this point on, he made an uneventful recovery. His temperature reached a normal level on February 28. The white blood cell count taken on March 1 was 7,500 with 45 per cent polymorphonuclears. The blood sulfadiazine level was 9.2 mg. per cent on February 28.

Case 3. M. G. L. was admitted on March 25, 1943 in a critically ill condition. He was in a state of mental confusion so that a complete history could not be obtained until three days later. The only complaint that could be elicited on admission was that of severe headache. Subsequently, he said that he had gone to bed the evening of March 24 feeling perfectly well. At midnight he was awakened with a severe chill and then developed fever. In the morning, he felt very dizzy, became extremely weak, and developed a headache which became progressively worse.

Examination was completely negative except for a marked purpuric eruption over his back, upper chest, and all extremities. His blood pressure was 60 mm. of Hg systolic and 40 mm. diastolic and his temperature was 103° F. A white blood cell count was 11,150 with 93 per cent polymorphonuclears of which 2 were myelocytes, 22 were juveniles and 30 were "stab" forms. The spinal fluid showed 2 lymphocytes, a sugar level of 77 mg. per cent and no increase in globulin. Culture of the fluid was negative. A Group I meningococcus was grown from the blood on March 26.

This patient was recognized as representing an early stage of the Waterhouse-Friderichsen syndrome. He was treated vigorously with sulfadiazine, intravenous glucose in saline, intravenous plasma, intravenous adrenal cortical extract, and intramuscular desoxycorticosterone. Full details of this case will be reported in a separate communication.

His temperature gradually dropped until it reached normal levels on his seventh hospital day. The rash completely disappeared by the sixth hospital day. The blood pressure gradually rose until it reached 100 mm. systolic by the seventh hospital day and a diastolic of over 60 mm. by the thirteenth hospital day. The white blood cell count came to normal levels on March 31 with 6,600 and 74 per cent polymorphonu-

clears. His blood sulfadiazine level was 17.5 mg. per cent on March 26 and 18.8 mg. per cent on March 27.

FIG. 2. Purpuric eruption on the legs.

He made an uneventful recovery after the first week of his illness although he did develop a bilateral muco-purulent conjunctivitis on March 30, which cleared in several days.

Case 4. W. A. M. was admitted the night of April 14, complaining of chills and headache. While he was on furlough on April 7, he had a severe chill, followed

by a short bout of fever and slight headache. The next day he felt weak, but he saw a physician who told him he had malaria, although no blood studies were done. At about the same hour on April 9, 11, 13 and 14, he had similar bouts of chills and fever. He had taken one quinine capsule a day since April 9. In addition to these recurrent bouts of chills and fever, he had a painful right elbow on April 11 and on April 14, painful swellings of the right and left ankle.

On admission, he appeared slightly ill with a swollen ankle. He had a scattered macular rash, resembling rose spots, over his chest and extremities. His temperature was 101.6° F. with concurrent pulse and respirations. A blood culture was taken and a spinal tap was done. The spinal fluid showed 6 lymphocytes. No organisms were grown from it. Blood smears for malaria showed no organisms. The white blood cell count was 12,150 with 92 per cent polymorphonuclears, 8 of which were young forms.

Because the possibility that this might be another case of meningococcemia was recognized, he was placed on sulfadiazine although rheumatic fever and malaria were considered as possible diagnoses. On April 16, he had a blood sulfadiazine level of 10.0 mg. per cent.

After the chill the night of admission, he no longer had either chills or fever. By April 18, the rash had completely disappeared and the joints were completely normal. On April 21, the eighth day after admission, the blood culture showed a Group I meningococcus.

The remainder of the course was uneventful. The white blood count of April 17 showed 3,900 cells with 66 per cent polymorphonuclears.

Case 5. A. W. F. was admitted to the Station Hospital on April 29, 1943 because of pain in his knees. This was of 16 years' duration, and apparently followed an automobile accident in 1927. General physical examination was negative and a roentgenogram showed early osteoarthritis with an osteochondroma of the right knee.

On May 11, while awaiting discharge from the Army, he had a chill followed by a recorded temperature rise to 100.4° F. At this time a generalized reddish, maculopapular eruption with a violaceous background was seen. A spinal tap was done and a clear fluid with three lymphocytes was obtained. A blood culture was taken. The blood count which had shown 9,200 white cells with 66 per cent polymorphonuclear cells now showed 10,200 white cells with 74 per cent polymorphonuclears.

The next day more lesions were seen. The dermatologist stated "if this patient appeared in the clinic, we would probably call this insect bites or some other type of bite, but since he is a hospital patient, will have to put this in the erythema multiforme group." New groups of lesions kept appearing and in some instances the older lesions developed hemorrhagic centers. The muscles were tender.

The first blood culture was reported as showing no growth but, because of the persistence of a low grade fever and new skin lesions, a second one was done on May 17. This condition continued until May 27 when, after five days of incubation of a third culture taken on May 23, a Group I meningococcus was discovered.

During the 16 days he was observed, the initial diagnosis of meningococcus septicemia was abandoned and diagnoses such as periarteritis nodosa and subacute bacterial endocarditis were considered. Biopsy of one of the skin lesions for a possible periarteritis nodosa merely shows a non-specific dermatitis with scattered collections of round cells, some polymorphonuclears, and plasma cells without definite relations to the skin appendages or arterioles. Some hemorrhagic areas were present.

Although he had no fever the day the blood culture was reported as positive, he was placed on the usual course of sulfadiazine. The blood count on May 28 was normal, showing 8,100 white cells with 57 per cent polymorphonuclears. The sulfadiazine level was 8.7 mg. per cent on this day.

Recovery was uneventful.

Case 6. L. J. E. was admitted to the Station Hospital on May 11 because of nausea and vomiting. He had felt well until 6 p.m. of May 10 when he became nauseated and vomited his dinner. He had several more vomiting spells with residual upper abdominal soreness but he had no diarrhea. He had a moderately severe headache.

He looked acutely ill with a temperature of 99° F. but no pathological findings were found on physical examination. His admission diagnosis was acute gastritis.

That afternoon his temperature rose to 103° F. but his headache had disappeared. Slight nuchal rigidity was present and a few spots, like rose spots, were seen on his abdomen. A blood culture was taken. A spinal tap revealed a clear fluid with one lymphocyte, a sugar level of 84 mg. per cent, and a trace of globulin. The white blood cell count was 10,990 with 82 per cent polymorphonuclears.

The next day, May 12, his second in the hospital, he developed pain and slight limitation of motion in the phalangeal joints of his right middle three fingers. On the following day these joints became swollen, red, and tender. The skin lesions had not changed and no new ones had developed. Because of the joint findings, he was placed on salicylates. Two hours later, the laboratory reported that a gram negative diplococcus, which later proved to be Group I meningococcus, had grown in the blood culture. He was started on intravenous sodium sulfadiazine, 5 grams.

The joints began to clear the next day so that by May 15, only the right ring finger was still swollen. This finger improved slowly so that it was May 25 before it had complete motion.

The white blood cell count became normal on May 17 with 5,500 cells and 59 per cent polymorphonuclears. The sulfadiazine level was 12.5 mg. per cent on May 13. The temperature became normal on his eighth hospital day.

Case 7. J. C. M. was admitted on May 13, complaining of a severe frontal headache that was noticed that morning. For the preceding week he had felt tired. The night preceding admission, he felt chilly but had no true chill. He awoke the morning of admission feeling quite drowsy and with a severe headache.

On examination he had a few violaceous reddish macules, which disappeared on pressure on his upper chest and abdomen. Otherwise no pathological findings were noted. He did not appear ill.

His temperature was 100° F. with corresponding pulse and respiratory rates. A spinal tap showed 7 cells with 1 polymorphonuclear and 6 lymphocytes. The sugar was 66 mg. per cent and the Pandy was negative. A blood culture was taken. Sulfadiazine therapy was started because it seemed that this was another case of meningococcemia.

On May 15, a Group II alpha meningococcus was grown from the blood. The rash was completely gone by May 16. The blood sulfadiazine level taken on May 14 was 17.5 mg. per cent. The temperature became normal the day after admission and remained so until discharge from the hospital.

His entire course was uneventful.

Case 8. W. C. W. was admitted on June 1, complaining of cough and aching in both legs. He had been discharged from the hospital several days before, after having apparently recovered from an upper respiratory infection. He developed his muscular and substernal aches the day before admission. His nose was obstructed and he had a slight headache.

Examination showed only a congested nose and injected throat. His white blood count was 10,200 with 58 per cent polymorphonuclears. He ran an irregular course of fever with red, slightly tender, elevated spots on his chest and feet. On June 12, all the skin lesions had disappeared, the temperature was normal, and he felt well. On June 15, his temperature rose slightly, joint pains inconvenienced him, and several new skin lesions, this time looking like mosquito-bites, developed.

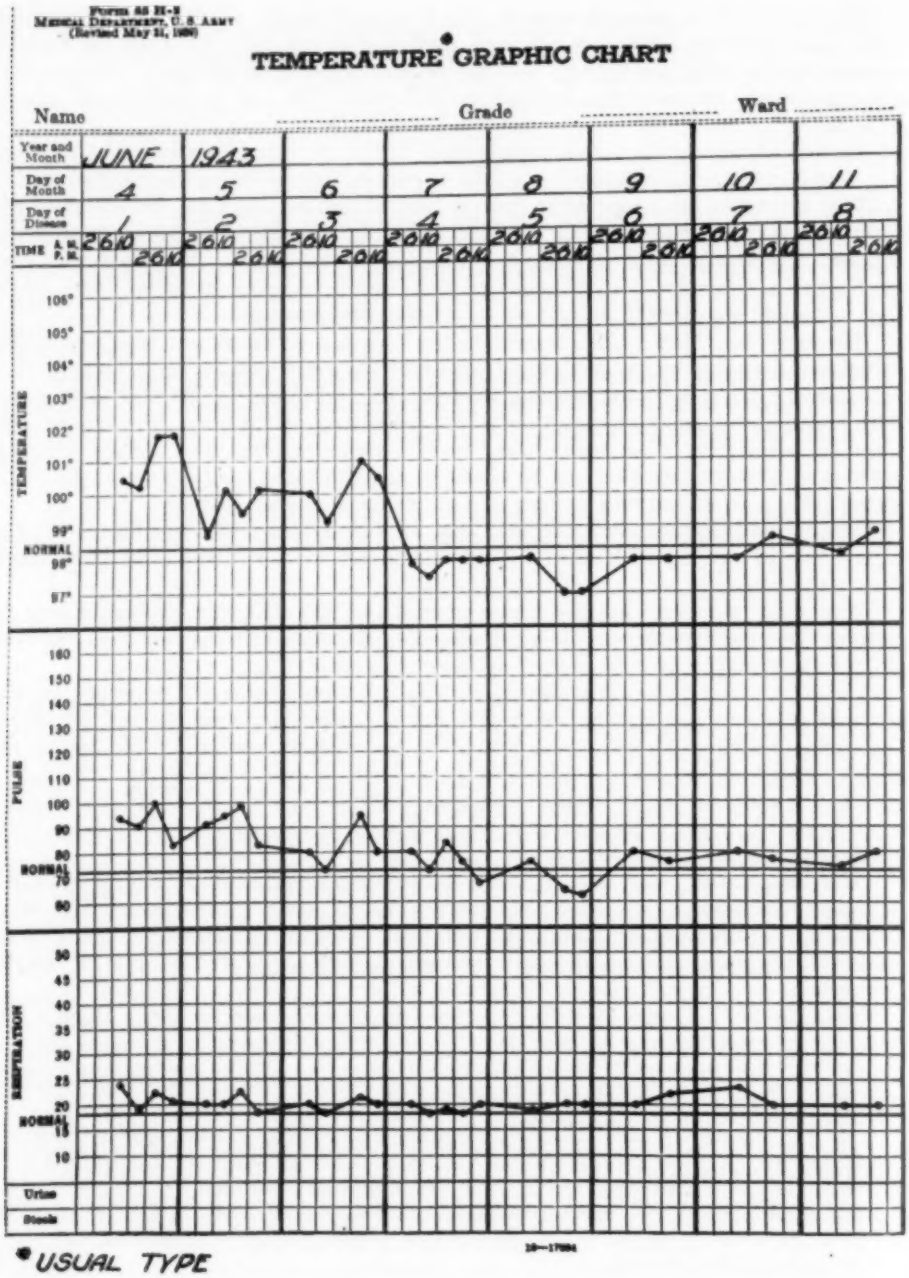

FIG. 3. Temperature chart from case of meningococcemia showing curve of usual type.

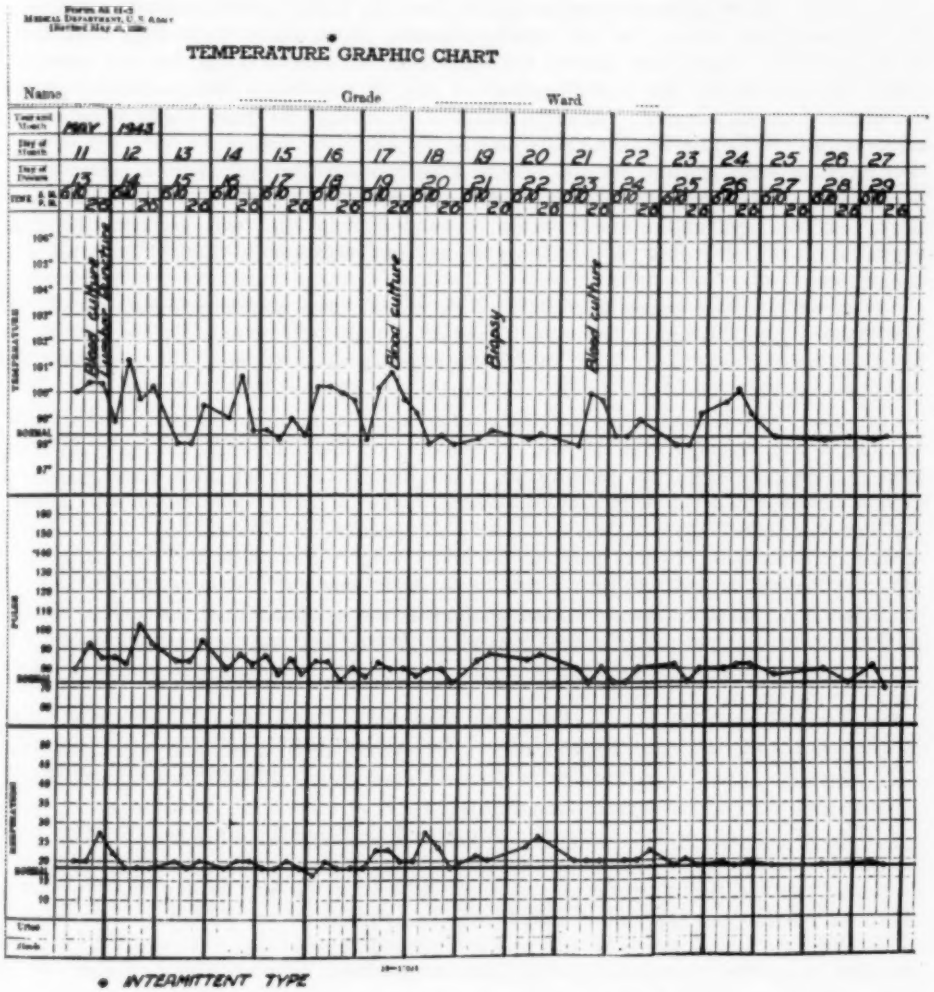

FIG. 4. Temperature curve of intermittent type.

On June 17, his temperature rose suddenly to 104.2° F. and a new painful lesion was seen on his left forearm. Physical examination otherwise still revealed no pathological findings but blood for culture was taken. The white blood cell count was 10,900 with 77 per cent polymorphonuclears of which four were young forms. The following day a Group I meningococcus was isolated from the blood. The rash became more widespread and now looked like those seen in previous cases of meningococcemia, round, pinkish macules with a violaceous background. A spinal tap showed 4 lymphocytes in the fluid which was sterile on culture.

Although the temperature had returned to normal by the time the blood culture report was received, he was placed on a course of sulfadiazine. The blood sulfadiazine concentration, 24 hours after starting therapy, was 10.8 mg. per cent. The white blood count on June 21 was 9,750 with 52 per cent polymorphonuclears. The rash completely disappeared by June 19 and his further course was uneventful.

Case 9. C. P. was admitted to the hospital on June 4, 1943, complaining of a frontal headache, aching in his muscles, bones, right ankle, both hips and both shoulders. His illness had started the afternoon of June 3 after he had returned from a 10 day leave. He took 40 grains of aspirin within six hours of the onset of his illness without any relief of the headache. The night of June 3 and 4, he had a severe chill. When he awakened on June 4, he noticed a rash.

Physical examination showed him to appear moderately ill with a temperature of 100.5° F. and corresponding pulse and respirations. His throat was injected. The neck was not rigid and a questionable bilateral Kernig sign was present. He had varied sized macules over his trunk, anteriorly and posteriorly, and all over his extremities.

The white blood count was 19,950 with 85 per cent polymorphonuclears, 12 of which were young forms. The spinal fluid was clear with three cells, two of which were polymorphonuclears. The spinal fluid sugar was 81 mg. per cent and no globulin was present. No growth was obtained on culture.

A blood culture was taken and the patient was placed on a course of sulfadiazine because it was assumed that he had a meningococcemia, although the ward surgeon stated, "eliminate erythema multiforme." On June 7, the blood culture had yielded a Group I meningococcus organism. On June 5, the day after medication was begun, the rash began to fade. It had completely disappeared by June 7. He had a blood sulfadiazine level of 9.6 mg. per cent 24 hours after the start of therapy. His temperature became normal on June 7 and he made an uneventful recovery.

Case 10. G. J. K. was admitted to the hospital on June 15, 1943 with a history of having had coryza for the two preceding days. The morning of admission his coryza had become worse and he developed a mild chill, malaise, sore throat, a slight cough and some frontal headache.

On examination he appeared slightly toxic with a temperature of 103° F. The only pathological physical finding was a congested nasal and pharyngeal mucosa. The white blood cell count, taken on June 16 was 15,450 with 81 per cent polymorphonuclears, 3 of which were young forms.

The day of admission he vomited once and then seemed to improve. His temperature reached 99° on June 17 and he felt well. On June 18, his temperature began to rise and he felt quite ill. His headache recurred and he developed a widely scattered maculo-papular rash on his trunk and extremities resembling mosquito-bites. Several hours later, some of the lesions formed hemorrhagic centers. The ward surgeon suspected meningococcemia and transferred him to the isolation ward. Sulfadiazine was started after spinal tap and blood cultures were done.

The spinal fluid showed 18 cells, 5 of which were polymorphonuclears and 13 lymphocytes. Culture resulted in no growth of organisms. A white blood cell count was 11,050; no differential count was done. The blood culture yielded a Group I meningococcus on June 21. The blood sulfadiazine level on June 20 was 12.0 mg. per cent.

The macules developed the typical violaceous background the next day, by which time the temperature had dropped to normal. It remained so for the rest of his hospitalization. The white blood count was normal on June 21. By June 22, the rash had completely faded and the remainder of his stay was completely uneventful.

Case 11. W. C. was admitted on June 30, 1943, complaining of pain in his chest, chills and fever, nausea and vomiting, and headache. He had had an upper respiratory infection for the week prior to his admission, with some nausea and occasional vomiting for the month preceding this. During the night he was awakened by a chill and pain across both sides of the upper part of his chest. He subsequently developed a severe headache.

His temperature was 102.2° F. and shortly after admission rose to 104°. Examination showed some impaired resonance over the left upper chest as the only pathological finding. Because the entire picture seemed to be one of pneumonia, a blood culture, sputum examination, and portable roentgenogram of the chest were done. The white blood cell count was 27,250 with 90 per cent polymorphonuclears of which 17 were young forms. The sputum did not contain sufficient pneumococci for typing. The roentgenogram was poor because of respiratory motion but a suggestive shadow extending from the right hilus towards the apex of the lungs was noted.

The next day the temperature came down to normal and the patient felt well. Subsequent roentgenogram showed the lung fields to be clear. On July 3, a Group I meningococcus had been isolated from the blood culture. Despite his apparent well-being and lack of any pathological physical findings, he was placed on a course of sulfadiazine. His blood sulfadiazine concentration after 24 hours was 7.3 mg. per cent. The white blood cell count on July 5 was 5,650 with 52 per cent polymorphonuclears.

He ran an uneventful course.

Most of the cases reported in the literature discuss the syndrome from its standpoint of chronicity, i.e. the length of time symptoms were present before the patient presented himself for study or before diagnosis was made. In all of our presented cases, symptoms were not present longer than two weeks before the diagnosis was made. Some of the cases had symptoms of upper respiratory infection for a short time before the acute onset. Case 1 had an upper respiratory infection for two weeks. Case 4 had chills and fever for one week before we saw him, and he was diagnosed as malaria elsewhere. This diagnosis has been made in previously reported cases. Case 5 developed his symptoms while in the hospital for another disease. His course, before the diagnosis was made, also simulated malaria. However, because the patient was seen throughout his course, other diagnoses such as subacute bacterial endocarditis and peri-arteritis nodosa were made in addition to meningococcemia. Case 6 had vague symptoms for a week prior to his acute onset. Case 7 had been in the hospital for an upper respiratory infection and had only been discharged a few days prior to his readmission. He ran a very irregular course for 16 days before acute symptoms suggested the possibility of meningococcemia. The symptoms in the other six cases began within several days of their admission to the hospital and the beginning of therapy.

The outstanding finding and the one which we have found most useful in calling our attention to the diagnosis is the skin eruption. Practically all the reported cases note the presence of some eruption. In only one case, number 11, was the rash absent. This case was also the most atypical in that it seemed to be a case of pneumonia on admission, and only because a routine blood culture was taken, was the organism found. In two cases, 1 and 3, the eruption was petechial and purpuric. Case 3 was a severely ill patient. The other eight cases presented variations of what we and others consider to be the basic type of eruption such as was seen in cases 7 and 9. This eruption is a round or oval macule or maculo-papule, pinkish in color and

with a violaceous background. It is generally found on the trunk and the extremities. We have never seen it on the face. In cases 4 and 6, it had more of a rose spot appearance because the lesion was smaller and the violaceous hue was missing. When the individual lesion develops a hemorrhagic center, it tends to look like the beginning form of the iris type of erythema multiforme. This was best seen in case 2. In three of our cases, instead of a purpuric center, this portion was raised and whitish, like a wheal, giving the lesion the appearance of a mosquito bite. Later the wheal disappears, a hemorrhagic area takes its place and the lesion resembles erythema multiforme. Cases 5, 8, and 10 illustrate this form. In only one case, number 8, did the lesion have any resemblance to erythema nodosum. The British case reports suggest that they have seen more of this type, i.e. a red, tender nodule. Our case, however, subsequently developed new lesions which were more typical.

The rash usually had begun to disappear by 24 hours after starting the drug and clears entirely in several days. The individual lesion gradually becomes brownish, smaller, and then disappears. Occasionally very slight branny desquamation is seen. In those cases with recurrent temperature rises, i.e. the malarial type, the lesions fade very rapidly and new lesions appear with each rise in fever.

The rash was also seen in a fair proportion of our cases which went on to develop meningococcus meningitis. A survey of about 50 cases of meningitis in which the organism was grown from the spinal fluid or blood or both revealed six cases which had a rash like that described above. However, in only one of these six cases was the blood culture positive. In the other five, the organism was grown only from the spinal fluid. Unfortunately we did not attempt to puncture the skin lesions to see whether or not meningococci were present in the macules. The only biopsy that was done on a skin lesion merely showed a non-specific dermatitis. Bacterial stains were not done because the search was for lesions supporting a diagnosis of peri-arteritis nodosa. Thus we cannot state whether meningococci in the skin are responsible for the lesions.

Joint and muscle pains form another outstanding characteristic of this syndrome. The various authors who have reported cases have noted this fact. In many instances it has been responsible for the confusion with rheumatic fever as occurred in our case 1.

In our 11 cases, five had no signs or symptoms referable to the joints. In three of the remaining six, there were complaints of pains in the joints and muscles. In case 5, there were not only muscle pains but these structures were quite tender to touch. It was this feature combined with other findings which suggested the diagnosis of peri-arteritis nodosa. In the remaining three cases, there was swelling, redness, and limitation of motion in the involved joints which included the small joints of the fingers as well as the large joints such as the ankles and elbows. These symptoms, in general,

cleared rather quickly under sulfadiazine therapy. In no case, was there any residual loss of function.

None of these joints was tapped. One of our meningitis cases did have a knee joint tapped after several days of sulfadiazine therapy. The fluid was purulent, no meningococci were cultured, and the sulfadiazine concentration in it was almost as high as the blood sulfadiazine level.

Schein [8] discussed this complication of meningococcemia in the pre-sulfonamide days. He reported three cases in which destruction of the involved joint occurred, but the general consensus is that such an outcome is unusual. It may very well be that such involvement may not occur when sulfonamides are used, particularly if the disease is recognized early, because recovery is rather rapid.

There were no outstanding neurological findings. Headache was the most frequent complaint. In seven of the cases it was severe enough to be a major symptom. In three it was slight and could have been part of the malaise that these patients experienced. One patient did not mention this symptom. In only one case, number 5, was slight rigidity of the neck noted. In two of the cases a questionable Kernig sign, which usually means a negative one, was elicited.

In 10 of the cases a spinal tap was done. No organisms were seen on direct smear nor were any organisms found on culture. There are no definite criteria for the cellular content of a normal spinal fluid. Todd and Sanford [9] state that 10 cells are usually accepted as the maximum number in health with nearly all being lymphocytes. On this basis, seven of our cases definitely fall into normal limits. Case 2 had five cells, two of which were granulocytes. This patient had a severe headache and a questionable Kernig sign. Case 9 had three cells, two of which were granulocytes. He had the same findings. These patients had short illnesses prior to the spinal tap and might have gone on to meningeal involvement with less intensive therapy. However, the sugar and globulin content in both of these fluids were normal. This, together with the fact that the further clinical course did not result in meningitis and that no meningococci were grown from the fluid on culture, leads us to include them as cases of meningococcemia without meningitis.

Case 10 had the greatest number of cells, 18, but only five were granulocytes. This patient, however, had only a slight headache and no neurological signs. Several days elapsed between the onset of symptoms and the performance of the spinal tap. The predominance of lymphocytes among the 18 cells, the absence of severe headache or neurological signs, also permits us to include this as a case of meningococcus septicemia without meningeal involvement. We have no explanation for the increased cell count other than the possibility of slight trauma while performing the tap and the counting of red cells as lymphocytes.

We have not experienced the difficulty reported by others in isolating the meningococcus. In one case, number 4, it took eight days before the

blood culture was reported as positive. In case 5, it took three blood cultures and a five day incubation of the third to isolate the meningococcus. In the other nine cases positive reports were returned in several days. We have not had to enrich the medium as has been suggested by practically all the other authors by adding ascitic fluid or other agents.

The technic for culturing the blood and spinal fluid has been as follows: The media used are: (1) pork infusion broth, (2) thioglycollate medium, Brewer,[10] (3) pork infusion agar and (4) chocolate agar. The infusion and broth and agar are prepared as described in Technical Manual, 8–227, War Department [11] using pork instead of beef or veal. (1) and (2) are inoculated at the bedside with 10.0 c.c. and 1.0 c.c. of uncitrated blood while blood agar plates are made by adding 1.0 c.c. of the citrated specimen to 10.0 c.c. of pork infusion agar in the laboratory. Cultures are incubated at 36° C. aerobically except for one blood agar plate which is placed in a Brewer anaerobic jar.

Sediment from centrifuged specimens of spinal fluid is inoculated with drops from a capillary pipette with a platinum loop into chocolate agar plates prepared from Dextrose Proteose No. 3 agar plus heated blood [12] and into thioglycollate medium.

All of the above media can be obtained in dehydrated form from supply houses or can be made from chemicals, ground meat and peptones, readily available. Heated blood used in making "chocolate" agar is the only enrichment material used.

That the above technic is adequate is evidenced by the fact that in only four cases of clinical meningococcus infection, with and without meningitis, out of more than 70 cases have we failed to isolate the organism.

Other laboratory findings were not characteristic.

All of our cases were treated with sulfadiazine. If the patient could not tolerate the medication by mouth, he was given 5 grams of sodium sulfadiazine intravenously followed by 1 gram every four hours, the route depending upon the patient's condition. If he could take the drug orally, the initial dose was four or six grams depending on his apparent condition. Fluids were given, as indicated, to assure a urinary output of 2,000 c.c. in 24 hours. Blood and urine examinations were done routinely to anticipate toxic reactions, but none was seen in our cases. The medication was continued, as a rule, for six to eight days and, in any case, until the temperature remained within normal limits for several days.

Our cases presented a wide variety of types. A malaria-like course was seen in two. Predominant joint involvement suggesting rheumatic fever was also present. One patient resembled a case of severe gastritis. Others presented varying pictures. Our last case had the clinical appearance of pneumonia and was recognized only because of a routine blood culture. Awareness of the possibility of the infection and the appreciation of the nature of the rash were the most important factors that enabled us to make

the diagnosis. The headache, though frequent, is too common a complaint to have a great deal of significance alone, but with the other findings, it is important.

Summary

1. Eleven cases of meningococcemia without meningitis are presented.
2. The diagnosis can be strongly suspected before the report of the blood culture in a patient with the skin eruption and headache if the possibility of this disease is kept in mind.
3. Sulfadiazine resulted in rapid cure without sequelae in all our cases.

Addendum

Since the above article was written, we have seen four additional cases of meningococcemia. In general, they tended to fall into the groups described above. One case had a temperature curve that was intermittent in type, whereas the other three had the usual course of fever for several days with a more or less sudden decline to normal after sulfadiazine was started. One case developed a rigid neck about 12 hours after the drug was started, but a spinal tap was not done. It was felt he had probably developed meningitis. His rash was entirely purpuric, and meningococci were demonstrated on examination of the tissue juice from his skin lesions.

Another patient had the macular type of lesions, some of which developed purpuric centers. Two of these on the foot became quite large and were ultimately seen as large bullous lesions. These are shown in figure 1.

The third had only macular lesions, from which meningococci could not be demonstrated in the tissue juice. The fourth had both purpuric and macular lesions but the latter predominated.

Figure 2 shows the distribution of the purpuric lesions as they appear on the extremities and, of course, give the name of spotted fever to the disease. It is lesions such as these that may make one consider typhus or Rocky Mountain spotted fever as a possible diagnosis.

All the cases recovered.

The attempt to demonstrate the organisms in the lesions is in agreement with the report made by Tompkins,[13] who demonstrated the organism in skin lesions of the purpuric variety but not in the macular variety. It may be that the macular lesions are a manifestation of toxin production, whereas the purpuric are due to destruction of the capillary wall by the organisms themselves. The macular lesions that develop purpuric centers may be due to a more intense action of the toxin or to the action of the organism after the toxin has acted. We hope to do more studies in future cases on the demonstration of organisms in the various skin lesions in these cases.

In three of the cases the first blood culture became positive in 24 to 48 hours. In the fourth case, a second blood culture had to be taken and was positive after 24 hours of incubation.

BIBLIOGRAPHY

1. Binns, J. F., and Fothergill, L. D.: Chronic meningococcic septicemia, New England Jr. Med., 1931, ccv, 536–539.
2. Carbonell, A., and Campbell, E. P.: Prolonged meningococcemia: report of three cases, Arch. Int. Med., 1938, lxi, 646–654.
3. Applebaum, E.: Chronic meningococcus septicemia, Am. Jr. Med. Sci., 1937, cxciii, 96–108.
4. Heinle, R. W.: Meningococcic septicemia: report of five new cases, Arch. Int. Med., 1939, lxiii, 575–583.
5. Moss, G. C.: Meningococcal infection with special reference to meningococcal septicemia, Med. Jr. Australia, 1941, i, 548–552.
6. Watson, L. D.: Meningococcemia without meningitis, case, New England Jr. Med., 1941, ccxxv, 685–686.

7. KATTWINKEL, E. E.: Meningococcemia, New England Jr. Med., 1941, ccxxiv, 685–686.
8. SCHEIN, A. T.: Articular manifestations of meningococcus infection, Arch. Int. Med., 1938, lxii, 963–978.
9. TODD, J. C., and SANFORD, A. H.: Clinical diagnosis by laboratory methods, 1942, Ninth Edition, W. B. Saunders Co., Philadelphia, Pa.
10. BREWER, J. H.: Clear liquid medium for "aerobic" cultivation of anaerobes, Jr. Am. Med. Assoc., 1940, cxv, 598.
11. Technical Manual 8–227: Methods for laboratory technician, War Dept., October 17, 1941, page 157.
12. REID, R. D.: Isolation and identification of the gonococcus, Bull. Johns Hopkins Hosp., 1942, lxx, 370.
13. TOMPKINS, V. N.: The diagnostic value of smears from purpuric lesions of the skin in meningococcic disease, Jr. Am. Med. Assoc., 1943, cxxiii, 31–32.

MEDICAL PROBLEMS IN THE MIDDLE EAST*

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THE medical problems in the Middle East Theatre of Operations which I will mention and discuss have either been published or mentioned on the radio; otherwise I could not discuss them. For the same reason of security, as it is called in the military service, it will not be possible to give specific rates concerning the incidence of these diseases among our troops.

I shall not include in this discussion anything about the fighting; or problems of evacuation of battle casualties, of which we had a considerable number in that theatre, as certain American units supported the Eighth Army in its advance across Africa from El Alamein to Tunis and into Sicily; but shall consider only problems pertaining to internal medicine.

As Surgeon of the United States Military North African Mission, and later as Chief Surgeon of the United States Army Forces in the Middle East, I was responsible for the organization and establishment of the medical service for all of our forces in the Middle East. There are now many American hospitals throughout the area from Tunisia through Tripoli, Benghazi, Cairo, the Levant, and on into Persia. Those were some of my hospitals.

In order to understand the distribution of the diseases encountered in this theatre, it will be necessary to consider the geography and climate because these factors affect disease. The Middle East is rather a large area. On an ordinary map, Africa and Europe are usually shown in order to include the countries in the Middle East; and, therefore, the countries look relatively small. The Middle East consists of Iran, Iraq, Turkey, Syria, Palestine, Transjordan, Saudi-Arabia, Egypt, Libya, Anglo-Egyptian Sudan, Eritrea and Ethiopia. The entire Middle East is much larger than the United States. The distance from an American hospital—for example in Persia—to one in Tunisia is over four thousand miles; much farther than it is from New York to San Francisco.

Many people think of Africa as a country of jungles. Actually, there is no jungle anywhere in the Middle East Theatre. The jungle in Africa is in West Central Africa. It does not extend into the Middle East or the North African Theatre areas. The countries of the Middle East vary, just as different parts of the United States vary from each other, as far as climate and the character of the country and the distribution of diseases are concerned. In the northern part of Persia, there are very high mountains, sixteen to eighteen thousand feet high. There is snow on these mountains even in the summer. On the other hand, in the southern and central parts of

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Persia, from the foot of the mountains down to the Persian Gulf, there is a desert with extremely high temperatures. Consequently, in different parts of Persia one may expect entirely different problems in health, and differences in the distribution of diseases. In the southern part of Persia, the so-called desert area, temperatures range from 135° to 145° in the summer. In Iraq, the Tigris and Euphrates Rivers join together to form the Shat-al-Arab. This country, particularly in the central and western portions, is desert. At the junction of the two rivers is the fabled site of the Garden of Eden, and a little farther to the west are the ruins of Babylon, which have been excavated. Evidence shows that at one time this part of the world was thickly populated and highly developed from an agricultural standpoint. Now it is only desert. There is also evidence to show that the depopulation occurred probably as a result of malaria.

Syria and Palestine farther to the west are entirely different from Iran and Iraq. There are mountain ranges parallel to the shore of the Mediterranean, and the country is highly developed and rich in agricultural land. The mountains are so high in Syria that skiing takes place as late as May. The climate along the Levant, as it is called, is almost ideal. In fact, it is quite similar to our California climate. Between the mountains and the sea, along the coastal plains, citrus fruit groves are found, particularly in Palestine. The coastal plain is rather thickly populated with many small villages and cities, including the beautiful city of Tel-Aviv on the coast of Palestine. In Palestine the modern buildings and relatively modern sanitation in the Jewish cities and towns which have been built within the last twenty years contrast with the mud hovels and total lack of sanitation among the Arabs and their villages.

Saudi-Arabia was of no particular concern to us. It is largely desert, sparsely inhabited, and the interior of the country is barred to Christians. Even aircraft travel over the central part, around Mecca, is forbidden lest it offend the Mohammedan people, who largely populate the Middle East. Egypt is entirely different from any other country in the Middle East. Although the chart shows it to be rather a large country, actually some fifteen million people are concentrated in a triangle about one hundred miles on each side. The triangle called the Delta is like a funnel and extends from Alexandria to Port Said and down to Cairo. There is a narrow belt of cultivated land along the Nile as it runs through Egypt. This belt which may range from a few hundred yards to three or four miles, is also thickly populated. The remainder of the country is largely made up of rocks, desert, and mountains which are entirely barren of all vegetation.

The Anglo-Egyptian Sudan is really a continuation of Egypt, as far as the character of the country is concerned. However, in the extreme southern parts there are marshes and swamp lands in which are found much large game. Eritrea and Ethiopia are very similar. They are very rugged countries with high mountains, again sixteen thousand to eighteen thousand

feet high. The country is primitive and so are the people. Considerable developmental work was done during colonization by the Italians who built some very beautiful cities and very fine roads. There is one spot in Eritrea, the seaport of Massaua, which is comparable in climate to Southern Persia. This port of Massaua has also a high humidity so that it is extremely difficult for Occidentals to live and work in that port continuously. The Italians had a rest camp up in the mountains about forty miles away to which they took their people several days each week.

Libya extends along the southern edge of the Mediterranean from the border of Egypt to Tunisia. Around Benghazi in what is called the Benghazi Hump, as far east as Derna, the country has been rather highly developed agriculturally by the Italians. The climate is pleasant. Tripoli, farther to the west, is a beautiful resort city, and the surrounding country for miles around has been highly developed. There are beautiful estates surrounding the city of Tripoli. Excluding the principal areas around Tripoli and Benghazi, the country is rocky and sandy, much like the country in Nevada and Utah. Although the temperatures were as high as 120° last summer in Tripoli, still the nights were cool and the climate on the whole is not unpleasant.

The eastern edge of Tunis as far north as the town of Enfidaville, a little way south of the city of Tunis, came within the boundaries of our theatre during the march to Tunis as the Middle East forces pushed up from the Mareth Line. The country along this eastern part of Tunis is not unlike some parts of Pennsylvania. There are wheat fields, orchards and many cattle. It is highly cultivated, and there are some very nice little cities. It was quite chilly in Tunis last May and June, and wool clothes were comfortable. This very brief and sketchy description of the various countries of the Middle East shows that it is far different from the country most of us ordinarily think of as constituting that part of the world. It is not terrifically hot all over the Middle East. Excessive heat occurs only in the two areas mentioned. There is no jungle and the desert is not just sand.

The environment, habits and ways of living of the people who inhabit this part of the world also determine the distribution of diseases with which we are concerned. All of this part of the world might be called the Arab world, as it is largely inhabited by Arabs. Most of these people are Mohammedans and therefore have certain customs which differ markedly from ours. The great majority of the adult natives throughout this part of the world are the survivors of many diseases. Owing to their habits, practically all of these people are exposed to typhoid fever, dysentery, malaria, sand-fly fever, smallpox and typhus. In one area the infant death rate as far as we were able to determine was eight hundred per thousand; in other words, eight out of ten babies died before they were a year old. In another area, three out of ten died before they were a year old, and half of the survivors died before they became adults. Most of them died, I think, of typhoid fever or dysentery.

Diseases of the intestinal tract, such as typhoid fever, bacillary dysentery and amebic dysentery are all prevalent throughout the entire middle east. The habits of the people are responsible for the almost universal infection of the population with these diseases which have such a high mortality among infants and little children. In fact, typhoid fever is considered a child's disease in the Middle East. As a result of the universal infection, the carrier rate among the survivors is exceptionally high.

These people do not use toilets and contaminate the ground along streams. A typical scene along any stream or canal will show individuals contaminating those banks or the stream itself with feces and urine. Then nearby there may be others washing their clothes and still others bathing. Then on down the stream there may be women dipping up the water which has been contaminated into large jars for drinking purposes or drinking out of their cupped hands directly from the stream or canal.

As another example, in one large city, relatively modern in as far as the buildings are concerned, the water supply is obtained from snows melting on the mountains. The water is brought down to the city in underground channels. However, when it reaches the city it is turned out into the gutters of the streets and there one may see people contaminating the water with human excrement, and bathing in the gutters, washing clothes and then drinking the water. In effect, these gutters are the combined water and sewage supply system of the city. Typhoid and dysentery, either bacillary or amebic, can be acquired only by taking into the intestinal tract in food or drink the organisms which have been excreted from the intestinal tract of others. The scenes just described illustrate one method of introducing these intestinal diseases into a large portion of the population.

However, another important method of dissemination in the Middle East is by the fly. Owing again to the contamination of the ground with fecal material, garbage, and refuse of all kinds as well, flies abound, and these flies which breed in this material contaminate their feet as they feed on the excrement of people who are carriers. Screening is practically unknown anywhere in the Middle East, and all the kitchens of the finest hotels are unscreened. The food becomes contaminated and you eat it and contract the disease.

A third method very common in the Middle East which also helps to spread the intestinal disease arises from the almost universal custom of irrigating gardens with sewage or highly contaminated water. It is unsafe to eat lettuce, radishes, raw celery, or any vegetable grown in the ground, or such things as strawberries, unless they can be cooked thoroughly in order to kill the bacteria which are on these vegetables as a result of the method under which they are grown. Amebic dysentery is most commonly transmitted by the eating of green vegetables which have been mechanically contaminated by human excrement either by direct fertilization or heavily contaminated water. For two years I did not have lettuce, radishes, or fresh strawberries or raw celery, and neither did I have dysentery.

In order to survive in the Middle East without contracting one of these intestinal diseases, it is absolutely necessary to follow certain simple rules, such as eating only thoroughly cooked food, or fruit which has to be peeled before it is eaten, by avoiding local ice cream or milk which has not been boiled. Americans are people with a great curiosity. When American troops first come to the Middle East and see a restaurant or a hotel which looks inviting, they'll go in and eat the things that are placed before them. As a result, immediately after every troop ship arrives, the sick rate for dysentery shows a sharp increase until that particular group of troops has been educated and discipline maintained in carrying out the very simple rules necessary to avoid dysentery or any of the intestinal diseases. We were able to demonstrate to the amazement of local health authorities that fly breeding could be restricted and that dysentery, typhoid and other intestinal diseases could be controlled at our bases in the Middle East.

Typhoid fever itself was not particularly a problem to our troops in the Middle East. All of our personnel are inoculated against typhoid, paratyphoid A and paratyphoid B, and this inoculation is most effective. However, dysentery was quite a problem, both bacillary and amebic. Where it was possible to make such surveys we found that the so-called "Gippy tummy," "Delhi tummy," "Teheran tummy" or "Massaua tummy" were all mild cases of dysentery, usually Sonne or Flexner in type. The onset is usually with diarrhea which may be accompanied by abdominal cramps. The stools run as high as twenty to thirty in 24 hours, and they may show blood and mucus macroscopically—almost all show blood microscopically. If untreated, the patient becomes dehydrated and rather toxic. These mild cases will usually subside in a week to ten days if untreated, but relapses are very frequent. Under the treatment which was in force in the Middle East in 1941, that is, giving a saline cathartic followed by paregoric and bismuth, these cases would usually respond in from four to five days. The more serious cases, showing blood and mucus, frequently had a prolonged and stormy course in hospital, and there is an appreciable death rate from bacillary dysentery. Many of the cases spent from a month to sometimes as long as six months in hospitals. Supportive treatment, such as intravenous fluid, was necessary. We were able to get a small quantity of sulfaguanidine which was used to treat the more serious cases, with dramatic results. Later, as larger quantities of sulfaguanidine became available, it was found that many of the milder cases of dysentery could be treated without hospitalization. Patients who had twenty to thirty stools a day, when treated with sulfaguanidine, in from twelve to twenty-four hours showed a diminution in the number of stools to perhaps three or four in twenty-four hours. The patients immediately became less toxic and often felt so well that they wanted to go back to duty. The very mild cases usually responded to treatment without hospitalization, simply spending a day in bed. The average quantity of sulfaguanidine required was one-quarter of a pound per patient for a large series of cases. Sulfaguanidine changed the entire picture of

the treatment of dysentery in the Middle East. Instead of being a disease which filled the hospital beds with patients for relatively long periods of time, with many of the patients seriously ill, our non-effective rate—that is, the number of patients in hospital constantly—was markedly reduced and the days spent in hospital were very few compared to previous experience. There were very few relapses among the dysentery cases treated with sulfaguanidine. Shortly before I left, sulfadiazine was being used also with excellent results in the treatment of bacillary dysentery.

A fairly large number of cases of amebic dysentery was found in routine stool examinations which were required of all patients entering hospitals for any cause. Many of these patients were absolutely symptom free or had only periodic attacks of mild diarrhea which were not severe enough to cause them to apply for medical attention. Amebic dysentery was particularly prevalent in Persia. The standard emetin treatment gave excellent results. Mixed infections of bacillary and amebic dysentery are more frequent than might be expected. Often the case coming in with severe diarrhea, prostration, blood and mucus when treated with sulfaguanidine would apparently clear up and then relapse after a few days. Stool examination showed amebae and treatment for amebic dysentery then was in order. *Entameba coli* was very common, and we had considerable difficulty initially in training laboratory technicians to differentiate between *Entameba coli* and *Entameba histolytica*. Initially, many cases of *Entameba histolytica* were reported which, when checked by well trained personnel, were shown to be *Entameba coli*. It was necessary to send a specially trained laboratory officer to all of our hospitals to give training to laboratory officers and technicians in this differentiation before the confusion between *Entameba coli* and *Entameba histolytica* could be cleared up. Of course many of our medical personnel in this country have had little experience in the identification of amebae in stools.

The hazard of malaria is by no means universal in the Middle East; in fact, the problem of malaria is fairly well localized. For instance, a highly malarious area exists in southern Persia along the Shat-al-Arab and Persian Gulf shore. It exists there primarily because that limited district is highly irrigated and full of date palms, as the packing and shipping of dates is the principal industry there. Places where mosquitoes breed abound, and the natives are infected. Most of the children acquire malaria either as babies or early in life after their first year and either die or recover from the clinical symptoms; that is, chills and fever. However, they still carry the plasmodia in their blood. Therefore, when troops enter an area, if the natives are allowed to come into our camps to work with our troops and live near our troops, if these natives are carriers of malaria; and if, at the same time, the species of Anopheles mosquitoes which can transmit malaria are present, then a high malaria rate among our troops can be expected. Malaria in the Middle East existed around the Persian Gulf and in Southern

Persia. It exists in the Jordan Valley in Palestine and up along the rivers of Syria and it exists along the Suez Canal and in the Egyptian Delta, and along the entire length of the Nile River. It exists in certain areas in Eritrea. It was said to occur around Benghazi and Tripoli and along eastern Tunis, but we found that it did not exist there. In only one place, a little town called Gabes, did we find malaria along the north coast of Africa east of Tunis. Malaria can be controlled under those conditions and we did control it. It is impossible to drain all the swamps or irrigated areas during a military operation. Neither is it economical to drain acres and acres of swamp when you may only be there a short time. The simplest and most satisfactory solution there was to train our troops in what we call malaria discipline—measures the individuals can take to protect themselves from the bites of an infected mosquito; such as repellents, the use of mosquito bars, and, where possible, screening of buildings. The simplest means was to keep the natives at least a mile or two away from our camps, because Anopheles mosquitoes may abound and still there will be no malaria unless there is some infected person within a mile or so who has previously been bitten by this Anopheles mosquito. An Anopheles mosquito ordinarily does not fly more than a mile. We did not use suppressive drugs in the Middle East theatre.

A number of cases of malaria acquired on the west central coast of Africa developed clinical symptoms after arriving in the Middle East. This malaria was malignant tertian. It might be well to emphasize the fact that malaria rivals syphilis as the great masquerader. It behooves all physicians in this country to become familiar with the symptomatology and the multitude of manifestations of malaria. Many of our men returning to this country are having, and will have, relapses. The importance of this is illustrated by two cases that occurred early in our experience. One case was a young man who had arrived in the Middle East from a highly malarious area about four days before his illness. He reported on sick call to a young doctor who also had recently arrived from the United States, actually from the northeastern part of the United States where malaria is not a problem. This patient complained of diarrhea and abdominal cramps with typical symptoms of "Gippy tummy" or a mild case of bacillary dysentery. This young doctor made the diagnosis of diarrhea, clinically. This patient was treated with magnesium sulphate, followed with paregoric and bismuth. There was no fever, no chills, no headache. The patient was marked "Quarters" and was put to bed. About eight hours later, this young physician was called by another soldier who stated that the patient had collapsed and was unconscious. The patient was immediately moved to the hospital; intravenous quinine therapy was started after a smear showed malignant tertian malaria. He died about two hours later. An autopsy showed the vessels in his brain filled with plasmodia.

The other case was also a young man who had arrived within less than a week and also complained of diarrhea and lassitude. He was seen by a

young medical officer who had had little experience with malaria. He was treated for his diarrhea with the usual saline purgative, followed by paregoric and bismuth. The man improved and was returned to duty. At no time did he have chills or fever or complain of a headache. The second night after being returned to duty, investigation showed that he got up to go to the latrine. He was found dead the next morning. Autopsy showed the usual picture of the cerebral type of malignant tertian malaria. It was necessary to issue instructions to examine a blood film for malaria in all men who had been in a highly malarious area who presented themselves on sick call or complained of headaches or abdominal symptoms. We made a survey of approximately one hundred men who had come across by air from west central Africa which is highly malarious, and found positive smears in 30 per cent of individuals without symptoms. All of these individuals were placed on a therapeutic course of treatment.

Another disease in the Middle East, called Pappatacci or Sand Fly Fever, is found throughout Persia. It exists in the Levant to a lesser extent. It is found in Egypt and in Libya. It was not a problem in Eritrea and Ethiopia. Like malaria, this disease is transmitted by an insect, in this case a sand fly. Before the sand fly can become infected, it must first bite an individual who is carrying the virus in his blood. If after a period of four to seven days, the sand fly bites another individual, it injects this virus into his blood stream. After a period of time he develops a terrific headache, fever and other symptoms of sand fly fever. A sand fly ordinarily doesn't fly more than 50 to 100 yards, and a person can be bitten by millions of sand flies and never get sand fly fever unless first they have had the opportunity of biting an individual who carries the virus in his blood.

The transmission of this disease is well illustrated by a small epidemic which occurred among our troops. In one locality it was convenient to place a battalion near the railroad yards, and barracks were built right across the street from a row of native mud and stone huts. These sand flies breed in piles of stone and mud—rubble it is called. Thus there were excellent breeding grounds for the sand fly right across the street. The natives furnished the reservoir of carriers because they carried in their blood the virus which causes sand fly fever. The sand flies that had become infected by biting the natives then flew across the street 50 or 75 feet, and bit our soldiers who sat around outside of the barracks in the evenings. Those barracks were screened; that is, the windows were screened with a wire netting called "sand fly screening," but in constructing the buildings they didn't put any screen doors on, only solid wooden doors and the soldiers in the hot weather naturally left the solid wooden doors open. That was a perfect setup for sand fly fever, and at the first outbreak an investigation was made as to the cause and it was perfectly obvious how it was being acquired. The necessary remedies were applied—and they were very simple ones indeed—and the epidemic was stopped. We found that oil sprayed on the ground

around buildings is an excellent repellent as far as sand flies are concerned. Screening of buildings—complete screening, including doors, that is—is also an excellent method of control. We do not have adequate knowledge about sand fly fever. It is known that carriers do exist in large numbers but how long an individual can remain a carrier after he has had the disease, is not known.

The diagnosis of sand fly fever is not satisfactory as it is made largely by the process of elimination. An individual who comes in with a severe headache, post orbital pain, general aching, high fever, who has no obvious localized infection such as a cold, tonsillitis, etc.—and who shows no malaria in blood smear, is diagnosed sand fly fever. I am not sure but that many mild influenza cases were confused with sand fly fever. A better method of diagnosing this disease was needed and a Neurotrophic Virus Disease Commission headed by Dr. Paul, of Yale University, is now in the Middle East, working on sand fly fever. They are attempting, first, to develop a diagnostic serological test for the disease; and second, to determine how long individuals may remain a carrier of the virus of sand fly fever. The text-books we found were not accurate in some of the statements made about sand fly fever, particularly the duration of its possible carrier state. We were, of course, also interested in the method of controlling this disease. It is hoped that as a result of the work of this Commission our knowledge concerning sand fly fever will be increased.

Dengue is a disease which exists in the southern part of the United States. It was a problem in the Middle East only in one locality, around the harbor of Massaua. Dengue, like malaria, is transmitted by a mosquito, an Aedes. To become infected, the mosquito must first bite an individual who is carrying the virus in his blood. Owing to the fact that the particular area in which dengue existed was small, an insect control unit was put in the area and was able to control this particular type of mosquito. As a result of the work of the insect control unit, our troops did not become infected.

Typhus is another disease prevalent in the Middle East. It is a disease closely associated with war. During and after a war, people, particularly refugees, are crowded together. People come into communities where war work is being carried on and crowd together, particularly in cities. Under such overcrowding, people lack adequate bathing facilities and in the Middle East bathing is not too common anyway. Epidemic typhus is spread by lice which abound among these people and are transmitted from one individual to another.

Typhus is a very important disease which migrates with people, principally refugees. After the last war it was reported that approximately 10,000,000 people had typhus as a result of war conditions. The death rate is frequently very high. Large epidemics of typhus did occur in Egypt, and in Persia there was a small outbreak. We had reports that typhus had broken out in Tripoli, and when we captured that city we found some; but

again, by keeping the natives away from our troops or our troops away from the natives, by placing the infested part of cities out of bounds, preventing our troops from entering the infested areas or having contact with infected people, typhus can be prevented, and we didn't get any large number of cases of typhus among our troops.

Fortunately the United States of America Typhus Commission was in my theatre. It carried on extensive work on the efficacy of certain control measures among the native population. We believe that we have a very effective means of controlling typhus among our troops, and are most optimistic about the control of typhus. Epidemic typhus was found largely in Egypt; a mixture of epidemic and murine typhus in Eritrea and Ethiopia. Murine typhus prevailed in Syria where it is endemic; there was both epidemic and murine typhus in Persia and Iraq where it is also endemic. The entire Middle East may be regarded as an endemic area for typhus, either epidemic or murine typhus. We learned some very interesting things about typhus and I saw personally a good many hundred cases. This Commission studied also the clinical course of the disease, the complications and the pathology, and their findings will be published later.

Yellow fever is another disease of importance. The yellow fever belt extends across Central Africa to the Red Sea. The disease has migrated from the west coast to the east as a result of religious pilgrimages to Mecca, and we were very much interested in the possibility of an outbreak of yellow fever in Eritrea, which would have been a serious thing for American forces there. The *Aedes egypti* were found there in large numbers.

Dr. Mahaffey, who has done so much work in Africa [with the Rockefeller Commission] on yellow fever, was brought in to Eritrea, and he obtained many blood samples from natives. Mouse protection tests were done, and it was found that yellow fever had been present in Eritrea. Very strict precautions were therefore required. Quarantine regulations were placed into effect in the spraying of planes going into uninfected areas in the Middle East, from the yellow fever areas and the potential yellow fever areas. We have a very efficient vaccine now for yellow fever, and it has been widely publicized that our troops going into such areas have been inoculated. We are happy to report we have had no yellow fever cases among our troops. However, that does not in any way permit a relaxation of vigilance so long as our aircraft travel through the yellow fever belt, and passengers, who of course include other than military personnel who have been inoculated, go into and out of that area. There is the ever present danger of infected mosquitoes being transported by air into non-endemic areas and causing foci of yellow fever to develop in various parts of this world. We kept a very close watch on the spread of yellow fever.

Plague, like most of these tropical diseases, is also carried by an insect, in this case by the rat flea. An epidemic of plague in the Middle East itself was observed to migrate from an initial focus in one port to four different widely separated ports, as a result of infected rats boarding these ships and

then infecting other rats at the other ports. The fleas left the dead bodies of the rats which died of the disease, got on human beings and infected them, and they died of bubonic plague. These certain cities were placed completely out of bounds as far as American troops were concerned. An investigation of the epidemic showed that it was the pneumonic type with 100 per cent mortality in the particular ports in which the epidemic occurred.

Infectious hepatitis is another very interesting disease which is endemic throughout the Middle East, particularly in the Levant and along the northern coast of Africa. It was a very important disease because if it strikes troops in large numbers those troops are unable to fight. It not only affected our own troops but those of our enemy. Many Germans and Italians were left to be prisoners because they were too ill with infectious hepatitis to be moved.

In the Levant, infectious hepatitis was sometimes called the "immigrant disease" because people coming into that country almost universally become infected. Much remains to be learned about the disease. The mode of transmission is not known, whether it is transmitted by means of flies or by a blood-sucking insect such as the mosquito, or perhaps the sand fly. It is known that the virus is in the blood, particularly in the preicteric stage, and that it can be transmitted to others by direct inoculation of the blood. The incubation period is extremely variable, from two weeks to three or four months, as has been determined by inoculation experiments. It is known, too, that individuals may carry the virus in their blood and, as far as known, not develop the symptoms until a precipitating factor occurs, such as fatigue or reduced rations. In general, lowered resistance to any type of infection may precipitate the clinical symptoms in individuals who have been carrying the virus for long periods of time. The initial symptoms are usually anorexia and a resulting loss of weight. Then jaundice develops, and there is usually nausea and vomiting. There may be hematemesis, delirium and mental confusion. There is an appreciable death rate. The period of hospitalization on the average is relatively long, from four to six weeks, and that is an important factor in a military organization, particularly if a relatively large number of troops develops infectious hepatitis during an epidemic. Among our troops the disease was observed in all degrees of severity from the mildest infection with only anorexia and a slight icteric tinge to quite severe cases who required a long period for convalescence. The treatment used was a high carbohydrate high vitamin B diet. A study has been made of the epidemiology of one outbreak and a commission has been working on the problem of how this disease is transmitted because the answer to that problem will enable us to control it. Epidemiological observations together with the fact that the virus is present in the blood and can be transmitted by direct inoculation lead me to believe that it is borne by blood-sucking insects, possibly mosquitoes or sand flies. I rather suspect the *Aedes egypti* because after an unusual so-called wind-borne flight of these mosquitoes into an area in which certain troops were located, an outbreak of infectious

hepatitis subsequently developed. It is not known how long a man may be a carrier of this disease. Since there is the possibility that individuals may return to the United States carrying the virus of infectious hepatitis in their blood, there may be outbreaks here.

It is well known that trachoma occurs in the United States in certain areas. It is very common in certain parts of the Middle East, principally in Egypt, where the infection rate is as high as 95 per cent; in fact, the infection rate is almost as high as that of intestinal diseases. When you see little children with their eyes literally plastered with flies, the reason that the infection is almost universal is not difficult to explain. The doctors who have spent years treating the natives agree almost entirely that it is mechanically borne by flies. It was no problem as far as military forces were concerned. We developed not one case because we have not lost our sensitivity to flies resting on our skin, particularly on our eyes. Occidentals go around brushing the flies away from their faces. There may be a factor of racial susceptibility concerned in the high rate among the natives; however, I think the habits and living conditions of the people rather than the racial immunity are the important factors in this disease.

The so-called exotic diseases of the tropics that fill our textbooks on tropical diseases have fascinating names; that is, names that are fascinating to us in the profession—schistosomiasis, dermal-leishmaniasis, kala-azar.

Schistosomiasis is the most important disease in Egypt from an economic standpoint. The infection rate is very high and the ability of individuals with Schistosomiasis to work is limited. I have seen hundreds of cases in native hospitals. There are a few small areas in the Levant where Schistosomiasis is found but the largest area of what might be called endemically epidemic Schistosomiasis exists in the delta and along the highly irrigated margins of the Nile River. I have seen urine that was practically pure blood and spleens that looked like watermelons and were hard as rocks. Schistosomiasis was not a problem among our troops.

A statistical survey of diseases which are prevalent in a country in which you are going to move troops is not enough. The habits of the people and their environment must be studied in order to determine whether or not the diseases that are endemic in that area will affect your troops. Schistosomiasis is a disease that demonstrates this point. Why is this disease a problem among the natives, a problem of course to the doctors, both missionary and others, who are taking care of the natives? Why is it no problem at all to the military forces? This is partly because of the habits of the natives urinating and defecating along the banks of the canals and streams, in which the snail, the intermediate host, is present. It is also because the native spends day after day working in his irrigated fields up to his knees in muck and mud and highly contaminated water. It is because of his economic status and his way of living that he has Schistosomiasis. He makes his living working in irrigated land, land which is repeatedly inundated. This disease is no problem to our troops—first because we placed out

of bounds all fresh water streams and prohibited our troops from entering the areas in which Schistosomiasis is prevalent. A few cases occurred among the troops of one of our allies who disregarded the advice of their medical officers, and one engineer unit tried to practice river crossing on one of the canals and a few cases of Schistosomiasis developed. We had no cases among American troops nor do I expect that there will be any because our troops do not live like the natives.

A little common sense in prohibiting wading and bathing in fresh water streams in the endemic area prevents the infection as far as our troops are concerned. That is why a statistical survey was not sufficient in determining the probable hazard of this disease to our troops.

Dermal leishmaniasis occurred in wounds. The so-called tropical or desert sore may be dermal leishmaniasis, or it may be staphylococcic or streptococcic infection, or it may be a dermal diphtheria infection. Some studies would indicate that dermal leishmaniasis can be mechanically transmitted by flies from one lesion to another. By the use of antiseptics and dressings on the slightest scratch, we entirely prevented dermal leishmaniasis in our American troops. We were able to protect our troops from the sand fly which transmits the systemic type of leishmaniasis: kala-azar. Kala-azar was no problem, although it is widespread among the natives. We kept our troops away from the natives—that is, outside of flying range of infected or potentially infected sand flies, which is very limited.

Relapsing fever was a problem among some of the troops of our allies, particularly when they got into caves, but was not a problem among American troops.

Filariasis was not a problem in the Middle East as far as our troops were concerned. Although it is mentioned in the textbooks as being endemic, I saw no cases of it.

Venereal diseases are widespread throughout the Middle East, and it is interesting to note in Persia the prevalence of chancroid. The usual proportions of gonorrhea, chancroid and syphilis were badly disturbed in Iran. For security reasons I cannot give you the exact figures but I may say that chancroid was the most prevalent venereal disease in that area. Chancroid is mostly associated with filth. When one of our men developed gonorrhea or syphilis in that area, it could usually be traced to a woman of European descent, or at least partial European descent. Chancroid almost invariably came from a native woman.

One of the medical problems which was limited to the desert in the southern part of Persia, and Massaua in Eritrea, which is the extremely hot and humid harbor on the coast, was the effects of heat. It had been my fortune previously to spend several years in the tropics where I made a few studies on the effects of heat on the human body. The important real emergency is heat stroke and heat stroke can kill people very rapidly, so I established heat stroke centers in those areas and we were able to keep our mortality from

heat stroke very low. Heat prostration is very common, and we were able to control that largely by the use of salt.

Particularly interesting are the effects of prolonged exposure; that is, of being exposed to this heat for months at a time. I will describe briefly a few of the changes that take place. In an effort to get rid of body heat, the capillary beds and superficial blood vessels are dilated more or less continuously, and after a period of some months an apparent anemia develops; that is, a red cell count of three to three and a half million cells is normal. This is not due to a decrease in red cell production but to an increase of plasma, and the old idea of your "blood becoming thinned out in the tropics" is literally true. Also a hypotension becomes the rule. Individuals with hypertension with a systolic pressure up to 250 millimeters frequently show a fall to 135 or 140 millimeters. An individual who has a normal systolic pressure of 120 to 130 mm. frequently has a pressure scarcely reaching 100 millimeters of mercury after a few months. The diastolic pressure is only slightly lowered.

After some months of exposure, the development of these changes in the blood count and in the blood pressure results in the appearance of certain symptoms. These are the symptoms which might be expected with cerebral anemia or arteriosclerosis. The individuals become very irritable, they quarrel and fight over the slightest imagined insult; they become extremely forgetful, and I have seen individuals start out to see someone and forget whom they are going to see. It becomes almost a rule that you must write down everything in a notebook if you are to remember it longer than five minutes. Accompanying this irritability and forgetfulness, the inability to concentrate on a problem becomes very marked. Men complain that they are unable to do their work because they can't concentrate on it. There is nothing particularly new in this syndrome. However, few doctors recognize it as a clinical entity.

There is also a lowered resistance to all types of infection. The slightest scratch becomes a chronic sore. The infection rate of respiratory diseases, strange to say, is very high. These changes are not particularly new and have been studied by many others, but they are becoming increasingly important because for the first time in history we have large numbers of American physicians in these areas, where the prolonged exposure to the effects of heat must be dealt with. Those of you who are in teaching institutions, might advantageously present these changes, this clinical entity, if you care to call it that, to those students who may in the near future join the armed forces and be sent out to these areas, where they are to meet this problem. I first became interested in the disease myself from 1937 to 1939, when I made studies in Panama in an effort to determine the cause of a very high rate of respiratory infection there. I found it was due to the effects of heat. It is well to recognize that not all diseases, not all clinical entities are the direct result of infection, and that the effects of prolonged exposure to heat are as much a clinical entity as any other of the better known diseases,

such as vitamin deficiencies and metabolic diseases. It deserves the thought and scientific study of our internists, particularly in order that we may recognize that such a condition exists and establish certain criteria so that, if possible, individuals may be removed from prolonged exposure to heat before permanent damage is done. We might well call this clinical entity the "heat syndrome." It has no relation whatsoever to heat stroke or heat prostration which have been studied so thoroughly.

I have touched very briefly on some of the medical problems that I encountered as Chief Surgeon of the United States Army Forces in the Middle East over a period of two years. From a medical standpoint, as applied to military forces, the most important problems were the intestinal diseases, principally the dysenteries, both bacillary and amebic. Sand fly fever, infectious hepatitis, and in certain areas malaria, and the "heat syndromes," were also very important problems. Some of the problems that we feared as the result of our first statistical survey of the area, particularly the exotic tropical diseases, did not materialize, as far as becoming problems to our military forces. The young men who will graduate from our medical schools during the next few years and who are going to be sent all over the world and who will encounter these unfamiliar diseases need guidance and special efforts to prepare them to recognize, to control and to treat them. To those who are primarily interested in research, I present the problems of sand fly fever, infectious hepatitis and the "heat syndrome," all of which challenge our best efforts in scientific study.

HETEROPHILE ANTIBODY REACTION IN INFECTIOUS MONONUCLEOSIS *

By Robert E. Kaufman, Captain, Medical Corps, A. U. S.

The sheep cell agglutination test or heterophile antibody reaction, as it is also called, is a laboratory procedure of considerable value in clinical medicine. In this country one frequently speaks alternately of the Paul-Bunnell test; and in Europe it is often referred to as the Hanganutziu-Deicher reaction. In 1911 Forssman [1] recognized the nonspecificity of certain antigen-antibody reactions. The terms "heterogenetic," "heterophilic," or "heterophile" are applied to those antibodies that react with an antigen (sheep erythrocytes) which seemingly had nothing to do with their development. One type of heterophile antibody is known as the Forssman antibody, but there are other varieties of heterophile antibodies which differ from the Forssman type. It has been known for a long time that the serum of many normal persons is able to clump sheep erythrocytes in very low dilutions.[2] In 1924 Hanganutziu [3] noted high titers of heterophile antibodies in the sera of patients who had received injections of horse serum. These observations were confirmed two years later by Deicher.[4] Davidsohn,[5, 6, 7] in a series of publications, reported many more such instances, and further showed that the titer of heterophile antibodies is especially high if the horse serum injection is followed by serum disease.

During the course of a search for heterophile antibody responses in various clinical conditions, Paul and Bunnell [8] in 1932 discovered a high titer of such antibodies in the sera of several patients with infectious mononucleosis. Bunnell [9] later showed that this occurred in most cases of the disease and that it was sufficiently characteristic to be useful as a diagnostic aid. Numerous subsequent clinical reports [10, 11, 12, 13, 14, 15, 16, 17] emphasize the confirmative value of the sheep cell agglutination test in the diagnosis of infectious mononucleosis. Many investigations [18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29] have been conducted in the laboratories of Davidsohn, of Stuart, and of others, which ultimately proved that the heterophile antibodies in infectious mononucleosis were different in type from those found in normal serum and in the serum of patients who had received horse serum injections. The present concept is that there are three types of sheep cell agglutinins: those in normal serum, absorbed by guinea-pig kidney but not by beef erythrocytes; those in the serum of patients with infectious mononucleosis, absorbed by beef erythrocytes but not by guinea-pig kidney; and those in the serum of

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individuals treated with horse serum, absorbed by both guinea-pig kidney and beef erythrocytes.[17]

Various modifications [12, 23, 30, 31, 32, 33] of the Paul-Bunnell test have been suggested in order to make the test more rapid or more sensitive. Whereas the Paul-Bunnell method requires overnight incubation before final reading, the newer Davidsohn technic,[31, 32] which is very delicate, makes use of smaller amounts of material and requires only two hours' incubation. The Paul-Bunnell and the Davidsohn methods are the two standard procedures in this country at the present time. The differential test of Davidsohn consists of three parts: (*a*) agglutinating action of the patient's serum on sheep cells; (*b*) the same after absorbing the heterophile antibody with guinea-pig kidney; (*c*) the same after absorbing with beef erythrocytes. Thus, a typical result in a case of infectious mononucleosis would be reported as follows: "(*a*) serum, non-absorbed 1:448; (*b*) serum absorbed with guinea-pig kidney 1:224; (*c*) serum absorbed with boiled beef erythrocytes: no agglutination."

Technic

Practically every experienced laboratory worker who performs many sheep cell agglutination tests has made certain minor modifications in the recognized technics. Dr. Annis E. Thomson has done over 2000 of these tests by the Davidsohn method,[31, 32] unmodified until October, 1939, since which time the following changes have been in effect. First, instead of inactivating the serum for 30 minutes at 56° C., it was inactivated for four minutes at 61° C. Second, instead of reading the results of the agglutination after incubating for two hours at room temperature and again after overnight in the icebox, the final results were read after centrifuging at high speed for five minutes and then shaking thoroughly with the fingers. A carefully controlled series of tests showed that the two methods give essentially similar results. Third, instead of absorbing sera for one hour, five minutes were found to be sufficient, if the tubes were shaken thoroughly during that time. This applies to both the guinea-pig kidney and the beef erythrocytes. Fourth, the expressions "one plus," "two plus," and "three plus" are not used; merely "positive" or "negative." Fifth, all results were read macroscopically, because after centrifugation there was not enough diagnostic difference to warrant the use of the microscope. The net result of these minor changes in Davidsohn's standard technic is that the test is simplified, is just as accurate, and withal gives considerably quicker results. In fact, telephoned reports can be given within one hour of the time of arrival of the serum in the laboratory, if speed of diagnosis is important, which it occasionally is in a questionable case of infectious mononucleosis thought to be acute appendicitis, meningitis, typhoid fever, mumps, diphtheria, etc. Moreover, so much time is saved by these modifications in technic that many more specimens can be examined in a day. A complete description of the technic will soon be published.[34]

TABLE I

Infectious Mononucleosis

In each case the agglutinin titers reported are (1) with untreated serum; (2) with serum after absorption with guinea pig kidney; and (3) with serum after absorption with boiled ox erythrocytes.

Case No.	Sex	Age	Time of Test After Onset of Disease															
			3rd–5th Day	6	7	8	9	10	11	12th–15th	16th–21st	22nd–30th	1–2 Mos.	2–3 Mos.	3–4 Mos.	4–6 Mos.	6–9 Mos.	9–12 Mos.
1	M	17	Neg.										Neg.				1:112 1:56 Neg.	
2	M	14						1:14 N.D. N.D.			1:28 N.D. N.D.							
3	M	41									1:56 N.D. N.D.							
4	F	27				1:16				1:64								
5	M	25		1:112 1:28 Neg.				1:112 1:28 1:14										
6	M	22							1:32				1:448 1:224 Neg.			1:112 1:28 Neg.		Neg.
7	M	14						Neg.			Neg.					1:56 1:28 Neg.		
8	F	11									1:28 N.D. N.D.	1:224 1:56 Neg.	1:56 1:7 Neg.			1:14 Neg. Neg.		
9	M	17					1:56 1:7 Neg.					1:112 1:56 Neg.					1:14 Neg. Neg.	
10	F	23						1:112 1:56 Neg.										
11	M	33					Neg.				1:224 1:56 Neg.						1:112 1:112 1:14	1:28 1:14 Neg.

TABLE I—*Continued*

Case No.	Sex	Age	Time of Test After Onset of Disease															
			3rd–5th Day	6	7	8	9	10	11	12th–15th	16th–21st	22nd–30th	1–2 Mos.	2–3 Mos.	3–4 Mos.	4–6 Mos.	6–9 Mos.	9–12 Mos.
12	M	31		1:56 1:14 Neg.			1:112 N.D. Neg.								1:28 Neg. Neg.			
13	F	31							1:112 N.D. Neg.									
14	F	13										1:224 N.D. Neg.						
15	M	1		Neg.									1:28 1:14 N.D.					
16	F	24	1:112 1:28 Neg.						1:112 1:14 Neg.							1:224 1:112 1:7	1:112 Neg. 1:56	
17	F	34	1:14 Neg. 1:14				1:112 1:56 1:7								1:56 1:28 Neg.			
18	M	27							Neg.		1:112 1:28 Neg.							
19	M	17		1:112 Neg. Neg.				1:7 Neg. Neg.				1:14 Neg. Neg.						
20	M	30		1:112 1:28 Neg.				1:56 1:14 Neg.					1:56 Neg. Neg.					1:7 Neg. Neg.
21	M	42			1:112 Neg. Neg.		1:112 1:56 1:14									1:28 Neg. Neg.		
22	F	31							Neg.			1:28 1:14 Neg.						
23	M	3							1:112 Neg. Neg.		1:112 Neg. Neg.							

TABLE I—*Continued*

Case No.	Sex	Age	Time of Test After Onset of Disease															
			3rd–5th Day	6	7	8	9	10	11	12th–15th	16th–21st	22nd–30th	1–2 Mos.	2–3 Mos.	3–4 Mos.	4–6 Mos.	6–9 Mos.	9–12 Mos.
24	F	5										1:56 1:14 Neg.						
25	F	2										1:112 N.D. N.D.						
26	M	7												1:28 Neg. Neg.				
27	F	41					1:14 Neg. Neg.				1:28 1:14 Neg.		1:28 Neg. Neg.					
28	F	45	1:28 1:14 Neg.				1:14 1:14 Neg.											
29	M	36									1:56 1:14 Neg.							
30	F	32									1:28 Neg. Neg.		1:56 Neg. Neg.		1:56 Neg. Neg.			
31	F	13										1:56 Neg. Neg.		1:28 1:14 Neg.				
32	M	25					1:56 1:14 Neg.				1:112 1:14 Neg.		1:28 Neg. Neg.	1:56 1:14 1:14		1:14 Neg. Neg.		
33	F	22						1:1792 1:1792 Neg.						1:112 1:112 Neg.		1:28 1:14 Neg.		1:28 Neg. Neg.
34	F	27								1:14 1:7 Neg.	1:56 Neg. Neg.		1:7 Neg. Neg.					
35	M	29							1:28 1:14 Neg.					1:28 1:14 1:7				

TABLE I—*Continued*

Case No.	Sex	Age	Time of Test After Onset of Disease															
			3rd–5th Day	6	7	8	9	10	11	12th–15th	16th–21st	22nd–30th	1–2 Mos.	2–3 Mos.	3–4 Mos.	4–6 Mos.	6–9 Mos.	9–12 Mos.
36	M	14					1:28 1:14 Neg.											
37	M	12									1:56 1:28 Neg.							
38	M	2									1:32	1:28 Neg. Neg.	1:112 Neg. 1:56	1:28 Neg. 1:28	1:56 1:7 Neg.			
39	M	30					1:112 1:56 Neg.											
40	M	5											1:28 Neg. Neg.					
41	F	21			1:224 1:112 Neg.													
42	F	28			1:56 1:14 Neg.					1:1792 1:1792 Neg.	1:3584 1:1792 Neg.	1:3584 1:1792 Neg.	1:896 1:448 Neg.		1:112 1:28 Neg.	1:56 1:14 Neg.		1:14 Neg. Neg.
43	M	28									1:56 1:14 Neg.		1:56 1:28 Neg.			1:7 Neg. Neg.		
44	M	13									1:448 1:224 Neg.				1:7 Neg. Neg.			
45	F	3											Neg.					
46	M	4					1:28 1:14 Neg.					1:28 Neg. Neg.						
47	F	6								1:28 Neg. Neg.								
48	F	27										1:56 1:28 Neg.						

TABLE I—*Continued*

Case No.	Sex	Age	Time of Test After Onset of Disease															
			3rd–5th Day	6	7	8	9	10	11	12th–15th	16th–21st	22nd–30th	1–2 Mos.	2–3 Mos.	3–4 Mos.	4–6 Mos.	6–9 Mos.	9–12 Mos.
49	M	27	1:14 Neg. Neg.				1:14 Neg. Neg.			1:28 Neg. Neg.	1:7 Neg. Neg.							
50	F	30						1:28 Neg. 1:7				Neg.	1:56 1:14 Neg.					
51	F	10								1:14 4:14 Neg.		1:28 Neg. Neg.	1:28 Neg. Neg.					
52	M	8											1:7 Neg. Neg.					
53	F	19	1:14 Neg. Neg.	1:28 1:14 Neg.			1:112 Neg. Neg.											
54	M	9									1:56 Neg. Neg.							
55	F	17	1:56 Neg. 1:56				1:28 Neg. Neg.											
56	F	15								1:7 Neg. Neg.	1:28 Neg. Neg.							
57	M	33	1:28 Neg. Neg.	1:28 1:14 Neg.					1:56 Neg. Neg.				1:28 Neg. Neg.	1:7 Neg. Neg.				
58	F	20								1:14 Neg. Neg.								
59	M	46												1:56 Neg. Neg.				
60	M	12	Neg.												Neg.			
61	M	12							Neg.		Neg.		Neg.					

TABLE I—*Continued*

Case No.	Sex	Age	Time of Test After Onset of Disease															
			3rd–5th Day	6	7	8	9	10	11	12th–15th	16th–21st	22nd–30th	1–2 Mos.	2–3 Mos.	3–4 Mos.	4–6 Mos.	6–9 Mos.	9–12 Mos.
62	M	35			1:7 Neg. Neg.				1:7 Neg. Neg.		Neg.							
63	F	22								1:7 Neg. Neg.								
64	F	20								1:64		1:1792 1:896 Neg.						
65	F	20						1:448 1:224 Neg.			1:224 1:224 Neg.							
66	F	42											1:28 Neg. Neg.	1:28 Neg. Neg.				
67	F	18									1:896 1:224 Neg.		1:224 1:56 Neg.	1:14 Neg. Neg.				
68	M	21			1:14 Neg. Neg.				Neg. Neg. Neg.	Neg. Neg. Neg.								
69	M	32											1:56 1:7 Neg.	1:224 1:28 Neg.	1:28 Neg. Neg.	Neg. Neg. Neg.		
70	F	3																1:56 1:14 Neg.
71	F	2	Serum not tested															
72	F	3	Serum not tested															
73	F	5	Serum not tested															
74	F	22									1:56 Neg. Neg	1:112 1:56 Neg.						
75	F	47	Serum not tested															

TABLE I—*Continued*

Case No.	Sex	Age	Time of Test After Onset of Disease															
			3rd–5th Day	6	7	8	9	10	11	12th–15th	16th–21st	22nd–30th	1–2 Mos.	2–3 Mos.	3–4 Mos.	4–6 Mos.	6–9 Mos.	9–12 Mos.
76	F	8		1:7 Neg. Neg.						1:7 Neg. 1:7	1:7 Neg. Neg.	1:7 Neg. Neg.	1:7 Neg. Neg.					
77	F	52											1:7 Neg. Neg.					
78	F	25	1:7 Neg. Neg.				1:7 Neg. Neg.				Neg.	1:7 Neg. Neg.						
79	F	21			1:7 Neg. Neg.			1:7 Neg. Neg.			1:28 Neg. Neg.		1:14 Neg. Neg.					
80	F	27												1:14 Neg. Neg.	1:56 1:14 Neg.	1:7 Neg. Neg.		
81	F	15										1:448 1:448 Neg.	1:448 1:448 Neg.	1:112 1:56 Neg.	1:14 Neg. Neg.			
82	M	30						1:14 Neg. Neg.				1:448 1:224 Neg.						
83	F	25	1:56 1:14 Neg.						1:112 1:28 Neg.									

TABLE II

Control Series

In each case the agglutinin titers reported are (1) with untreated serum; (2) with serum after absorption with guinea pig kidney; and (3) with serum after absorption with boiled ox erythrocytes.

Case No.	Sex	Age	Sheep Cell Test	Diagnosis
			Leukemia and Lymphoblastoma	
1	F	59	Neg. Neg. Neg.	Leukemia, chronic myeloid
2	M	58	Neg. Neg. Neg.	Leukemia, chronic myeloid
3	F	59	1:28 Neg. 1:28	Leukemia, chronic myeloid
4	F	57	1:14 Neg. Neg.	Leukemia, chronic myeloid
5	M	17	Neg. Neg. Neg.	Leukemia, chronic lymphoid
6	F	4	Neg. Neg. Neg.	Leukemia, acute lymphoid
7	M	46	Neg. Neg. Neg.	Leukemia, chronic myeloid
8	M	20	1:14 Neg. Neg.	Hodgkin's disease
9a	M	30	1:112 1:28 Neg.	Hodgkin's disease
9b	M	30	1:224 Neg. 1:56	Nine months later
10a	M	45	1:14 Neg. 1:7	Hodgkin's disease (?)
10b	M	45	1:112 Neg. 1:56	One week later
11	F	69	1:7 Neg. Neg.	Lymphosarcoma

TABLE II—*Continued*

Case No.	Sex	Age	Sheep Cell Test	Diagnosis
			Serum Injections	
12	F	3	1:28 Neg. Neg.	Scarlet fever, 12 days after serum
13	F	10	1:14 Neg. Neg.	Scarlet fever, 11 days after serum
14	M	8	1:112 1:56 Neg.	Scarlet fever, 10 days after serum
15	M	11	1:14 Neg. 1:7	Scarlet fever: serum sickness
16	M	13	1:7 Neg. Neg.	Scarlet fever: serum sickness
			Liver Extract Injections	
17	F	63	1:7 Neg. Neg.	Primary anemia
18	M	67	Neg. Neg. Neg.	Primary anemia
19	M	55	1:28 Neg. Neg.	Primary anemia
20	F	46	1:7 Neg. Neg.	Primary anemia
21	F	67	1:28 Neg. Neg.	Primary anemia
22	F	55	1:28 Neg. 1:7	Primary anemia
23a	F	33	1:112 Neg. Neg.	Primary anemia
23b	F	33	1:14 Neg. Neg.	Three weeks later

TABLE II—*Continued*

Case No.	Sex	Age	Sheep Cell Test	Diagnosis
			Respiratory Infections	
24	F	45	1:14 1:14 Neg.	Grippe
25	M	31	1:7 Neg. Neg.	Grippe
26	M	44	Neg. Neg. Neg.	Grippe
27	F	40	1:14 1:14 Neg.	Grippe
28	M	53	1:7 1:14 Neg.	Grippe
29	M	30	1:14 Neg. Neg.	Grippe
30	M	?	Neg. Neg. Neg.	Grippe
31	M	15	1:14 Neg. Neg.	Grippe
32	M	45	1:14 Neg. Neg.	Grippe
33	M	20	1:28 Neg. Neg.	Grippe
34	F	15	Neg. Neg. Neg.	Grippe
35	F	48	1:28 Neg. 1:28	Acute tonsillitis
36	M	46	1:14 Neg. Neg.	Asthma
			Miscellaneous Diseases	
37	M	30	Neg. Neg. Neg.	Pulmonary tuberculosis

TABLE II—*Continued*

Case No.	Sex	Age	Sheep Cell Test	Diagnosis
			Miscellaneous Diseases—*Continued*	
38	M	20	1:28 Neg. Neg.	Undulant fever
39	M	?	Neg. Neg. Neg.	Trichiniasis (?)
40	M	35	1:28 Neg. Neg.	Rheumatic fever (?)
41	F	23	Neg. Neg. Neg.	Pyelitis, acute
42	M	42	1:28 1:7 Neg.	Syphilis; cholecystitis, acute
43	F	64	Neg. Neg. Neg.	Vitamin B deficiency
44a	M	19	1:56 Neg. Neg.	Rubella
44b	M	19	1:14 Neg. Neg.	Five days later
			Healthy Normals	
45	M	23	Neg. Neg. Neg.	
46	F	58	1:7 Neg. Neg.	
47	M	48	1:28 Neg. Neg.	
48	F	42	1:28 1:7 Neg.	
49	F	18	1:14 Neg. Neg.	
50	F	19	1:28 Neg. Neg.	

TABLE II—*Continued*

Case No.	Sex	Age	Sheep Cell Test	Diagnosis
			Healthy Normals—*Continued*	
51	F	18	1:28 Neg. Neg.	
52	F	20	1:14 Neg. Neg.	
53	F	19	1:7 Neg. Neg.	
54	F	18	1:14 Neg. Neg.	
55	F	19	1:28 Neg. Neg.	
56	F	19	1:7 Neg. Neg.	
57	F	18	1:7 Neg. Neg.	
58	F	20	1:28 Neg. Neg.	

CLINICAL

During a three year period 83 proved cases * of infectious mononucleosis have been investigated and are included in this paper. In the diagnosis of this disease there are three aspects to consider: the clinical, the hematological, and the serological. It is felt that if any two of them are definite, the diagnosis may be considered established. In this series were seen no cases positive clinically and serologically, but with consistently negative blood smears. However, there were many cases positive clinically and hematologically, but with negative serological findings, and a few cases positive hematologically and serologically, but with a subclinical or a very atypical clinical picture. The clinical and hematological aspects of infectious mononucleosis will not be discussed in this paper, since little could be added to Bernstein's excellent and exhaustive review.[17]

Sheep cell agglutination tests were done on the sera of all but five of our

* I wish to thank the following physicians for referring some of these patients for study: Drs. Abram Abeloff, Charles Bogoshian, Frederick Castrovinci, Lawrence Crawley, Carl Goldmark, Jr., Irving Kohn, George Laporte, Jr., Carl Reich, Armin St. George, Robert Schleussner, Nathan Serlin, and Irwin Sobel.

83 patients by Dr. Thomson.* The Paul-Bunnell technic was employed for one patient (case 4), and four patients (cases 71, 72, 73, 75) had no serological tests performed. I studied the blood smears of all 83 patients and also examined the patients with but few exceptions. In the cases not personally examined, the histories as reported by other doctors were carefully reviewed.

We were interested in performing the heterophile antibody reaction as frequently as was feasible in order to determine the variations in the titer with time. The results of these tests are shown in table 1. Also included is a control series (table 2), consisting of normal individuals; patients who had received liver extract injections for primary anemia; patients who had received horse serum for diphtheria or scarlet fever; and patients suffering from serum sickness, leukemia, Hodgkin's disease, and various miscellaneous conditions.

Discussion

What titer of heterophile antibody constitutes a positive test? That depends on various factors, the most important of which is the exact technic employed, including the method of reading the result, whether macroscopic or microscopic; the time interval, whether after two hours or after overnight incubation or after five minutes centrifugation; and the method of recording the degree of the reaction, "one plus" or "three plus" agglutination. It also depends on how one records the dilution. The differences in the dilutions of serum recorded in various publications make it very difficult to compare titers with each other. For example, Paul and Bunnell [8] call their first tube 1:4 (whereas it is in reality a 1:16 dilution of serum); Davidsohn [31] designates his first tube 1:7; and Bernstein [11] his first tube 1:20. Finally, another consideration seems to be the opinion of the author, based on his technic and experience. The lowest figure which may be called positive varies with different writers on this subject from 1:8 [10] through 1:32,[8, 9, 11, 16, 17, 35] 1:56,[31, 35, 36] 1:64,[37, 38] 1:320,[29] up to 1:512.[39] It should be pointed out that the extreme figures (1:8, 1:320, 1:512) were obtained with technics not now in general use. The two methods in common use in this country are the Paul-Bunnell and the Davidsohn. Most authors follow the originators of these methods in calling the lower level of positivity 1:32 with the former and 1:56 with the latter technic. The latter figure is considered positive by Davidsohn and most others only if the differential absorption is "correct"; i.e., if there is little absorption of heterophile antibody with guinea-pig kidney and complete absorption with beef erythrocytes.

From our experience and a review of the literature, we agree with Demanche [14] that the borderline between negative and positive cannot be very definitely stated. There are too many variable factors even with the well

* Dr. Thomson has performed the test on the sera of a great many other patients with infectious mononucleosis; but these cases are not included in this paper as they were not studied clinically and hematologically by me.

recognized technics, especially since most investigators have varied the technic in some particulars. If definite figures are to be given, however, we feel with many others that with the Paul-Bunnell technic a value of 1 : 32 or more is positive, and we would add that 1 : 16 is suggestive, requiring further investigation. We consider that with the Davidsohn technic, especially as modified by us, 1 : 56 or more is positive and even 1 : 28, provided that in the latter instance the differential absorption is "correct." The figures for the Davidsohn method refer to the macroscopic reading after overnight incubation in the icebox or, as we now do it, after centrifugation for five minutes. Smeall,[40] using the Paul-Bunnell technic, found only 0.4 per cent of 765 normal sera with an agglutination above 1 : 32.

With borderline results, the clinical and hematological features should be taken into consideration. Even with definitely positive sheep cell agglutination tests, the clinical picture must be considered as a whole in making a final diagnosis in an individual case. There are false-positives with this test just as with other laboratory procedures, such as the serological reactions for syphilis,[41] which are usually considered quite dependable. Among other things which must be known in interpreting a borderline or positive test in connection with the patient's present illness is whether he had recently been given serum or liver extract injections and whether he may have had infectious mononucleosis at any time within the past 12 months in clinical or even subclinical form.

With the foregoing limitations, a positive sheep cell agglutination test naturally is a strong point in the diagnosis of infectious mononucleosis, especially if the agglutination occurs in a high dilution and with the "correct" differential. However, as table 1 shows and as others [16, 17, 42, 43, 44] have also found, a negative test does not by any means rule out the diagnosis, even if the test is repeatedly negative. It is merely one point against the diagnosis; but if the clinical and the hematological pictures are definite, it is believed that the diagnosis is established. And we do not agree with Davidsohn [31] that it is necessary or desirable to separate seropositive from seronegative cases of what is considered to be the same disease.

The percentage of cases of infectious mononucleosis with negative sheep cell agglutination tests varies a great deal in different series of reported cases. This depends mainly on three factors: (*a*) the figure which the author considers necessary for a test to be called positive; (*b*) the frequency with which blood samples are tested in individual cases; (*c*) and most important, the number of cases of infectious mononucleosis which the author refuses to recognize and include as such because they have negative heterophile antibody reactions, even though they are "indistinguishable from infectious mononucleosis clinically and hematologically," in the words of certain authors. It is felt that these cases must be included in a discussion of the accuracy of the test. Van Ravenswaay,[35] for example, stated that all 16 of his cases of infectious mononucleosis had positive tests. However, 21 other

cases thought to be infectious mononucleosis before the agglutination test was performed were excluded because of negative tests. It would seem more correct to say that 16 of 37 cases or 43 per cent had positive reactions. Demanche [14] had 100 per cent positives in a series of 57 cases, but if seven other cases excluded only because of negative tests are included, his percentage falls to 89 per cent. The percentage of cases with positive agglutination tests varies in different series [9, 10, 14–17, 35, 37, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53] from 43 per cent to 100 per cent, with most authors reporting 80–90 per cent. Paul [16] said: "Ninety per cent of our cases had positive serology. This may indicate that we are relying too much upon the sheep cell test for our diagnosis." I agree with that interpretation.

In this series of 79 serologically tested cases we found that 51 were definitely positive (1:56 or more); eight were borderline (1:28 with the "correct" differential); and 20 were negative. Since we feel that 1:28 with the "correct" differential is also a positive test, our series shows 74.7 per cent positive cases. It is apparent from a glance at table 1 that the number of positive cases depends to some extent on when and how often one takes blood for the test. For example, one patient (case 7) was negative on the tenth and eighteenth days, but positive five months after the onset (with no intervening illness). In this series are included all cases in which we made a final diagnosis of infectious mononucleosis, whether the agglutination test was positive or negative. In fact, three children and one adult from whom blood was not obtainable are included, since the clinical and hematological pictures were very definite. This is correct, it is believed, especially since it happened that all three children had siblings ill at the same time with similar symptoms and blood smears and positive agglutination tests. I must admit that a few cases studied were excluded because of a negative test in the presence of clinical and hematological pictures which were suggestive but not entirely characteristic. These cases would have been included if the agglutination test had been positive. Since there are false-positive and false-negative sheep cell tests, and since the clinical and hematological pictures of infectious mononucleosis can be so variable, one must not be too dogmatic in any statements concerning this remarkable disease. Incidentally it should be noted that the titer of the sheep cell agglutinins bears no relation to the severity of the disease. Patients have been seen with reactions positive in dilutions of 1:1792 or 1:3584, although they were not ill enough to be kept in bed.

It is of clinical interest to know how soon in the disease the sheep cell agglutination test may become positive and how long it may remain so. In this series, one patient (case 16) had a definitely positive reaction as early as the third day of illness; one (case 55) on the fourth day; one (case 28) on the fifth day; and many others on the sixth day. Werlin, Dolgopol and Stern [50] had one patient with a positive reaction on the second day of illness. Bernstein [17] found a strongly positive test on the third day in one patient,

as did McAlpin.[54] Friedemann and Beer [10] record a positive test on the fourth day in one patient; Worms and Demanche [55] in one; and Bunnell [9] in two. Positive reactions have frequently been seen on the fifth and sixth days.[9, 15, 17]

As illustrations of the fact that the sheep cell agglutination test may not become positive until late in the disease in certain cases, we may observe from table 1 that case 1 was negative on the forty-fifth day and positive when retested during the sixth month; case 7 was negative on the twentieth day and positive during the fifth month; case 8 was negative in the third week and positive in the fourth week; case 30 was negative on the sixteenth day and positive on the fortieth; and finally case 50 was negative on the thirtieth day and positive on the thirty-eighth. None of these patients had any illness intervening between the last negative and the first positive tests. Himsworth [56] reported a case with a negative Paul-Bunnell test on the thirtieth day and a positive test during the third month. Bernstein [17] suggests that if the agglutination reaction is not positive at the end of one month from the onset of symptoms one can consider that it will not become positive. Some of the cases in this series show that the time limit cannot be so definitely set.

The test may remain positive for a long time, as some of these cases show. Case 1 was still positive serologically at six months; case 11 at seven and 11 months; cases 16 and 42 at six months; and case 70 at about 12 months, although the last case should perhaps not be included as I had not followed the course of the illness, but made the diagnosis in retrospect. Davidsohn [31] found positive tests lasting at least as late as the third and fourth months in two cases; Demanche [57] as late as four and a half months; and Sohier, Parnet and Bernier [49] past the third month. Apparently we have found a few cases in which the agglutination test remained positive longer than had previously been considered the upper limit. It is important to know that this reaction may remain positive for many months, since when one performs the test as an aid in diagnosing a febrile illness, it may be positive not as a result of the present illness, but of an attack of infectious mononucleosis many months before. A confusing situation arose in the case of a three-year-old girl (case 70) with unexplained fever and blood smears very suggestive of infectious mononucleosis. The sheep cell agglutination test was twice positive, yet the clinical diagnosis proved to be pneumococcus bacteremia (probably secondary to a pneumonia). In going into the past history carefully, we discovered from her pediatrician that she had had an illness 11 or 12 months before, which, considered in retrospect, was probably infectious mononucleosis. This would explain the suggestive smears and the positive heterophile antibody reactions, both of which may be present for many months, even for almost a year.

In summary of this aspect of the problem, it may be said that the sheep cell agglutination test usually becomes positive between the sixth and twenty-

first days of the illness, although sometimes earlier and sometimes not until much later or not at all. It usually remains positive for two to four months after the onset of the disease, although this is very variable, and it may return to negative much sooner or not until much later. As a rule, a positive test will be found for a longer period of time if the reaction was at some time positive in a high dilution. If only one diagnostic venepuncture is to be done, such as in children or in uncoöperative adults, it would seem best to do this not earlier than the ninth day nor later than the thirtieth day, and preferably between the twelfth and twenty-first days.

The sheep cell agglutination test has considerable value in clinical medicine, especially in febrile illnesses in which the diagnosis is not entirely certain. We feel that the test should be performed in fevers of unknown origin; in acute throat infections in which the diagnosis is not perfectly clear, such as in cases suspected of having diphtheria but in whom virulent Klebs-Loeffler bacilli are not found[50]; in patients with acute or subacute lymphadenopathy, local or generalized; in persons found to have an unexplained leukocytosis or leukopenia with a relative lymphocytosis or monocytosis, who may or may not be ill; in cases diagnosed as leukemia; and in definite or suspected cases of infectious mononucleosis. Also, as Bernstein[17] points out, in individuals with positive agglutination tests (Widal, etc.) without cultural confirmation; patients with false-positive Wassermann or similar reactions; individuals with unexplained acute abdominal conditions; patients with enlarged spleens, puffy eyelids or atypical forms of conjunctivitis; apparent cases of catarrhal jaundice, purpura hemorrhagica, Vincent's infection, aphthous stomatitis, benign lymphocytic meningitis, granulocytopenia. I agree with Demanche,[58, 59] Durupt,[60] and Bernstein[17] that the test may be of great value in these conditions, especially if positive; but I also agree with Lyght[61] that "the diagnosis [of infectious mononucleosis] can usually be arrived at in advance of the aid promised by the agglutination procedure. If sheep cell agglutination tests are readily available, of course, they may be employed as clinching evidence." It must be remembered that a negative test does not rule out the diagnosis of infectious mononucleosis, and conversely that a positive test does not definitely establish this diagnosis. In cases suspected of having infectious mononucleosis, the test should be repeated at intervals, and if the titer rises or if the test becomes positive after having been negative, the diagnosis is established beyond doubt, provided the patient did not receive an injection of horse serum a short time before.

As table 2 illustrates, an increased heterophile antibody titer may occasionally be found after the administration of serum (case 14) or liver extract (case 23); and in cases in which the final diagnosis is something other than infectious mononucleosis (cases 9 and 44). Bernstein[17] and Kent[62] record a few other instances of false-positive reactions. No explanation can be given for these false-positive reactions. In patients suspected of having leukemia, especially the acute form, the physician may save himself con-

siderable embarrassment by having a sheep cell agglutination test performed routinely before giving the family a fatal prognosis, as occasionally what was thought to be leukemia is later recognized as infectious mononucleosis when the serological test is reported positive (which it practically never is in leukemia) and when the patient makes a complete recovery.

Conclusions

1. Changes in Davidsohn's technic of performing the sheep cell agglutination test are described.
2. Tests were performed on 78 of 83 cases of infectious mononucleosis.
3. It is believed that agglutination in a dilution of 1:28 with the "correct" differential absorption tests is a positive reaction.
4. A positive test supports the diagnosis of infectious mononucleosis, but a negative test does not rule it out.
5. In this series, 75 per cent of the cases had positive reactions.
6. The reaction may become positive as early as the third day, but sometimes not until the second month or not at all.
7. The reaction usually remains positive for two to four months, although it may be nine to 12 months.
8. The test has considerable clinical value, especially if repeated at intervals in fevers of unknown origin.

BIBLIOGRAPHY

1. Forssman, J.: Die Herstellung hochwertiger spezifischer Schafhämolysine ohne Verwendung von Schafblut, Biochem. Ztschr., 1911, xxxvii, 78.
2. Davidsohn, I.: Heterophile antigens and antibodies, Arch. Path. and Lab. Med., 1927, iv, 776.
3. Hanganutziu, M.: Hémagglutinines hétérogénétiques après injection de sérum de cheval, Compt.-rend. Soc. de biol., 1924, ii, 1457.
4. Deicher, H.: Über die Erzeugung heterospezifischer Hämagglutinine durch Injektion artfremden Serums, Ztschr. f. Hyg. u. Infektionskr., 1926, cvi, 561.
5. Davidsohn, I.: Heterophile antibodies in serum sickness, Jr. Immunol., 1929, xvi, 259.
6. Davidsohn, I.: Further studies on heterophilic antibodies in serum sickness, Jr. Immunol., 1930, xviii, 31.
7. Davidsohn, I.: Heterophilic antibodies in serum disease: Third Report, Jr. Infect. Dis., 1933, liii, 219.
8. Paul, J. R., and Bunnell, W. W.: The presence of heterophile antibodies in infectious mononucleosis, Am. Jr. Med. Sci., 1932, clxxxiii, 90.
9. Bunnell, W. W.: A diagnostic test for infectious mononucleosis, Am. Jr. Med. Sci., 1933, clxxxvi, 346.
10. Friedemann, V., and Beer, P.: Die Hanganutziu-Deichersche Reaktion bei der Angina mit mononukleärer Reaktion (Monozytenangina), Deutsch. med. Wchnschr., 1933, lix, 440.
11. Bernstein, A.: Antibody responses in infectious mononucleosis, Jr. Clin. Invest., 1934, xiii, 419.
12. Butt, E. M., and Foord, A. G.: The heterophile antibody reaction in the diagnosis of infectious mononucleosis, Jr. Lab. and Clin. Med., 1935, xx, 538.
13. Davidsohn, I.: Infectious mononucleosis, Am. Jr. Dis. Child., 1935, xlix, 1222.

14. Demanche, M. R.: Le séro-diagnostic de la mononucléose infectieuse, Sang, 1938, xii, 86.
15. Foord, A. G., and Butt, E. M.: The laboratory diagnosis of infectious mononucleosis, Am. Jr. Clin. Path., 1939, ix, 448.
16. Paul, J. R.: Infectious mononucleosis, Bull. New York Acad. Med., 1939, xv, 43.
17. Bernstein, A.: Infectious mononucleosis, Medicine, 1940, xix, 85.
18. Davidsohn, I., and Walker, P.: The nature of the heterophile antibodies in infectious mononucleosis, Am. Jr. Clin. Path., 1935, v, 455.
19. Bailey, G. H., and Raffel, S.: Hemolytic antibodies for sheep and ox erythrocytes in infectious mononucleosis, Jr. Clin. Invest., 1935, xiv, 228.
20. Beer, P.: The heterophile antibodies in infectious mononucleosis and after the injection of serum, Jr. Clin. Invest., 1936, xv, 591.
21. Kemp, H. A., and Baker, B. O.: On the behavior of the heterophile antibody (hemagglutinin) of serum sickness and acute infectious mononucleosis to absorption with raw and autoclaved ox erythrocytes, Am. Jr. Clin. Path., 1936, vi, 560.
22. Davidsohn, I.: Isoagglutinin titers in serum disease, in leukemias, in infectious mononucleosis, and after blood transfusions, Am. Jr. Clin. Path., 1938, viii, 179.
23. Stuart, C. A., Burgess, A. M., Lawson, H. A., and Wellman, H. E.: Some cytologic and serologic aspects of infectious mononucleosis, Arch. Int. Med., 1934, liv, 199.
24. Stuart, C. A., Tallman, J., and Anderson, E. G. E.: Agglutinins for sheep and rabbit erythrocytes in human sera, Jr. Immunol., 1935, xxviii, 75.
25. Stuart, C. A., Tallman, J., and Brintzenhoff, E.: Sheep and rabbit cell agglutinins in horse serum sickness and infectious mononucleosis, Jr. Immunol., 1935, xxviii, 85.
26. Stuart, C. A.: Heterophile antibodies in infectious mononucleosis, Proc. Soc. Exper. Biol. and Med., 1935, xxxii, 861.
27. Stuart, C. A., Fulton, M., Ash, R. P., and Gregory, K. K.: The relations between certain heterophile antibodies and antigens, Jr. Infect. Dis., 1936, lix, 65.
28. Stuart, C. A., Griffin, A. M., Fulton, M., and Anderson, E. G. E.: Nature of the antibodies for sheep-cells in infectious mononucleosis, Proc. Soc. Exper. Biol. and Med., 1936, xxxiv, 209.
29. Stuart, C. A., Welch, H., Cunningham, J., and Burgess, A. M.: Infectious mononucleosis, Arch. Int. Med., 1936, lviii, 512.
30. Straus, R.: Simple slide and tube tests for infectious mononucleosis, Am. Jr. Clin. Path., 1936, vi, 546.
31. Davidsohn, I.: Serologic diagnosis of infectious mononucleosis, Jr. Am. Med. Assoc., 1937, cviii, 289.
32. Davidsohn, I.: Test for infectious mononucleosis, Am. Jr. Clin. Path., 1938, viii, 56.
33. Hollander, A.: The centrifuge technique in the heterophile agglutination test, Jr. Lab. and Clin. Med., 1940, xxv, 542.
34. Thomson, Annis E.: A rapid test for heterophile antibody in infectious mononucleosis—modified from Davidsohn's method, to be published.
35. Van Ravenswaay, A. C.: The heterophile agglutination test in the diagnosis of infectious mononucleosis, New England Jr. Med., 1934, ccxi, 1001.
36. Balgairies, E., and Christiaens, L.: Le séro-diagnostic de la mononucléose infectieuse, Paris méd., 1939, cxi, 493.
37. Boveri, R.: Über das Vorkommen heterophiler Antikörper bei lymphoidzelliger Angina, Klin. Wchnschr., 1933, xii, 666.
38. Kristensen, M.: Studies on the serologic diagnosis of infectious mononucleosis, Acta path. et microbiol. Scandinav., 1938, supp. xxxvii, 339.
39. Beeuwkes, H.: De Reactie van Paul en Bunnell, Nederl. tijdschr. v. geneesk., 1939, lxxxiii, 149.
40. Smeall, J. T.: Glandular fever (infectious mononucleosis), Edinburgh Med. Jr., 1942, xlix, 291.

41. KAUFMAN, R. E.: False positive serologic reactions for syphilis in infectious mononucleosis, Jr. Lab. and Clin. Med., 1941, xxvi, 1439.
42. GOUNELLE, H., and FOLLIN, S.: Mononucleose infectieuse avec rechute et syndrome digestif, Sang, 1939, xiii, 676.
43. DOWNEY, H., STASNEY, J., and MCKINLAY, C. A.: Infectious mononucleosis, Jr. Am. Med. Assoc., 1935, cv, 761. Discussion by Dr. I. Davidsohn.
44. ERF, L. A.: Acute infectious mononucleosis with unidentified structures in the supravital preparations of the lymph nodes, Jr. Mt. Sinai Hosp., 1936, iii, 113.
45. ROSENTHAL, N., and WENKEBACH, G.: Die Bedeutung der heterophilen Antikörperreaktion für die Diagnose der infektiösen Mononucleose, Klin. Wchnschr., 1933, xii, 499.
46. NOLAN, R. A.: Report of a so-called epidemic of glandular fever (infectious mononucleosis), U. S. Naval Med. Bull., 1935, xxxiii, 479.
47. BANG, O., and KRISTENSEN, M.: Kliniske Undersogelser over Forekomsten af Faareblodlegeme-Agglutinin (Heterofilt Antistof), Ugesk. f. laeger, 1936, xcviii, 1049.
48. DAVIDSOHN, I.: Personal communication.
49. SOHIER, R., PARNET, J., and BERNIER, G.: Diagnostic serologique de la mononucléose infectieuse par le test d'agglutination (réaction de Paul-Bünnell). Sa valeur pratique, Bull. et mém. Soc. méd. d. hôp. de Paris, 1939, lv, 846.
50. WERLIN, S. J., DOLGOPOL, V. B., and STERN, M. E.: Infectious mononucleosis—a diagnostic problem, Am. Jr. Med. Sci., 1941, cci, 474.
51. STRAUS, R., and BERNSTEIN, M. T.: Further serological studies in infectious mononucleosis, Am. Jr. Clin. Path., 1942, xii, 174.
52. CANZANI, R.: La suerologia de la fiebre ganglionar o mononucleosis infecciosa, Arch. urug. de med., cir. y especialid., 1942, xx, 104.
53. JOHANN, A.: Zur Frage der diagnostischen Verwertbarkeit der Hanganutziu-Deicherschen Reaktion beim Pfeifferschen Drüsenfieber, Ztschr. f. Immunitätsf. u. exper. Therap., 1941, c, 292.
54. MCALPIN, K.: Infectious mononucleosis, report of a case with 42,000 leucocytes, New York State Jr. Med., 1936, xxxvi, 908.
55. WORMS, R., and DEMANCHE, R.: A propos de la réaction de Paul et Bunnell dans la mononucléose infectieuse. Sa date d'apparition, Bull. et mém. Soc. méd. d. hôp. de Paris, 1939, lv, 1215.
56. HIMSWORTH, H. P.: Infective mononucleosis and the Paul-Bunnell test, Lancet, 1940, i, 1082.
57. DEMANCHE, R.: Evolution des réactions sérologiques au cours de la mononucléose infectieuse, Sang, 1939, xiii, 680.
58. DEMANCHE, R.: Le séro-diagnostic de la mononucléose infectieuse, Sang, 1938, xii, 86.
59. DEMANCHE, R.: Le diagnostic de la mononucléose infectieuse: Valeur des réactions sérologiques, Presse méd., 1939, xlvii, 1614.
60. DURUPT, A.: Le diagnostic sérologique des mononucléoses infectieuses, Presse méd., 1937, xlv, 1218.
61. LYGHT, C. E.: Infectious mononucleosis, Jr. Lancet, 1938, lviii, 91.
62. KENT, C. F.: "False" positive Paul-Bunnell (heterophile) reaction? Am. Jr. Clin. Path., 1940, x, 576.

"ATYPICAL" CORONARY DISEASE IN YOUNG PEOPLE*

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THE title "Atypical Coronary Disease" was selected advisedly, since the term coronary disease has long been used synonymously with coronary sclerosis (atheromatous). In this sense, disease of the coronary arteries on any other basis would be atypical.

Our interest in atypical changes in the vascular system as affecting the coronary vessels was stimulated by a series of 10 cases observed at the Station Hospital, Fort Ord, California over a three month period.

None of the patients died, so that in the absence of autopsy investigations, one can, at best, only postulate as to the pathology or its etiologic basis.

CASE REPORTS

Case 1. W. H. H. The patient was a 20 year old colored soldier who had been a blacksmith in civilian life and who had been in military service four months. His family history was not contributory. He had suffered severe sore throats as a child. There was nothing else pertinent in his past history. He denied any venereal history. He never smoked. He was admitted to the hospital on December 1, 1942, with the story that for the past five years he had been suffering attacks of precordial pain which had become worse in the past three months. The pain radiated to the left shoulder and down the left upper extremity and stopped either at the elbow or went down to the finger tips. The attacks usually came on with exertion or excitement and occasionally at rest. About three weeks before admission, he suffered an upper respiratory infection. On the day before admission he had a very severe precordial pain which lasted about an hour and left him weak and perspiring.

Physical examination was entirely negative except for a slight enlargement of the heart to the left and a transient soft apical systolic murmur. His blood pressure was 125 mm. Hg systolic and 80 mm. diastolic and remained at that level. There was no temperature elevation and no increase in the pulse or respiratory rate. The leukocyte and differential count remained normal, but the red cell sedimentation rate was very rapid and remained rapid for about eight weeks. The basal metabolic rate was ± 0; blood Kahn and Wassermann reactions were negative; blood sugar, 83 mg. per 100 c.c. of serum; blood cholesterol, 215 mg. Tuberculin test was negative and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 250 units. Electrocardiograms (figure 1) taken 48 hours after onset showed a depressed RT_2 and an inverted T_1, T_2 and T_3. Tracings taken 10 days after onset showed the RT_2 more depressed but a diphasic T_1. Tracings taken six weeks after onset show no RT depression, T_1 positive but depressed, and T_2 and T_3 inverted but less marked in degree. No QRS changes were observed at any time. The clinical course was uneventful.

Case 2. L. C. Patient was a 20 year old colored soldier who had been in military service 15 months. His family history was not contributory. He had

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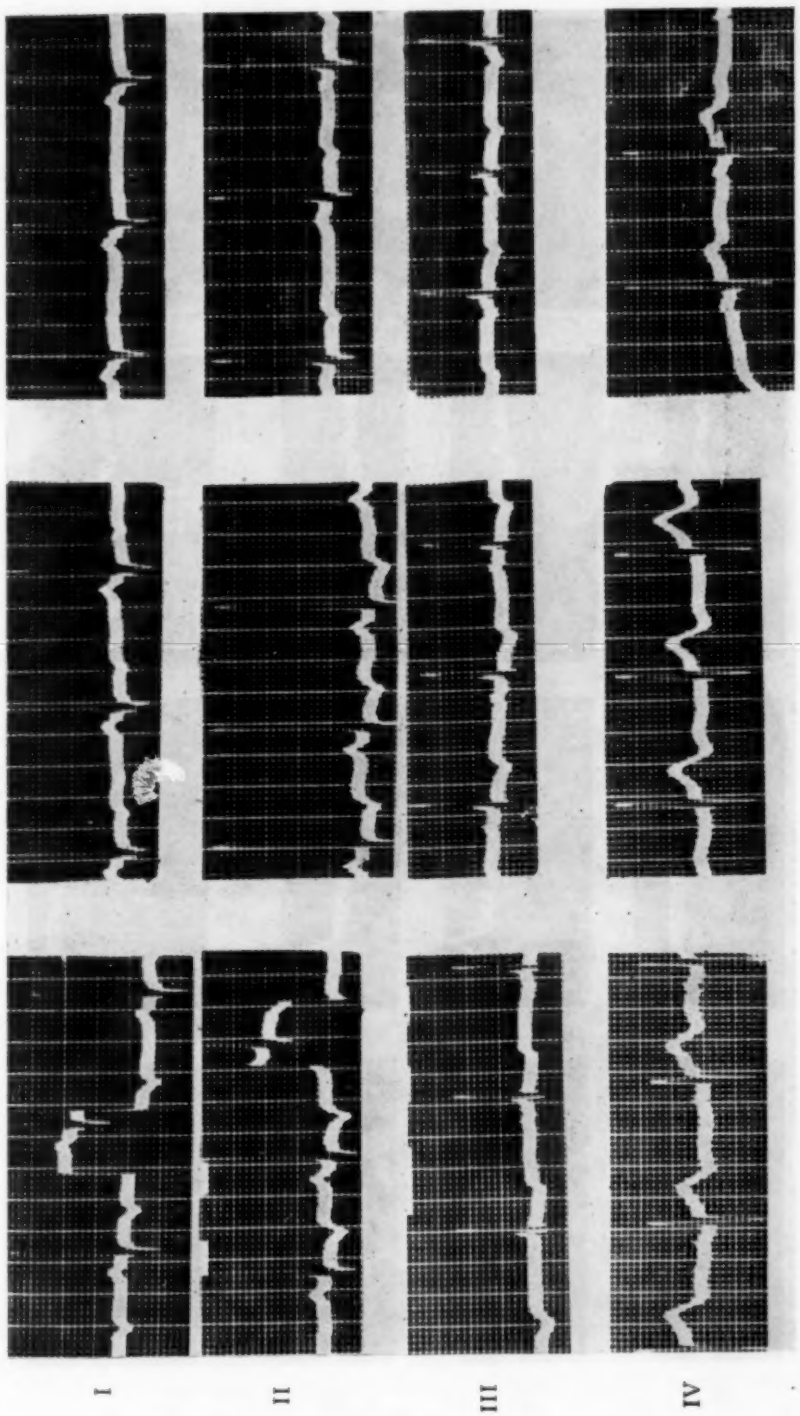

FIG. 1. Case 1.

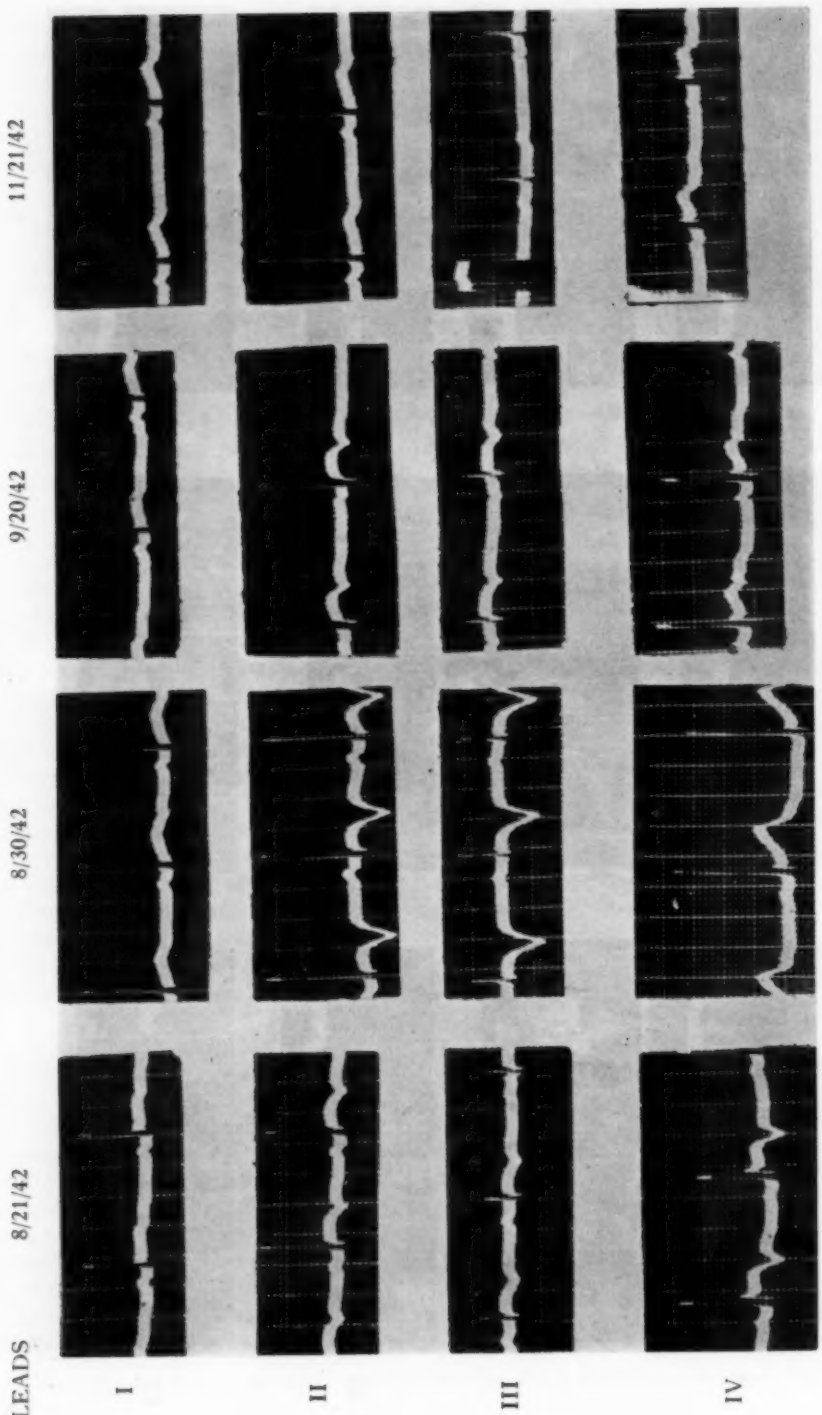

FIG. 2. Case 2.

suffered frequent sore throats as a child, and there was nothing else pertinent in his past history. He denied any venereal history. He was a moderate smoker. He was admitted to the hospital on August 19, 1942, with the story that four days before admission he developed a severe sore throat. He remained on duty, but on the third day he developed substernal pain. It was very severe for one day and persisted for about three days.

Physical examination was entirely negative except for inflamed tonsils and pharynx. The heart was not enlarged, sounds were of good quality, and no murmurs or friction râles were heard. His blood pressure was 122 mm. Hg systolic and 80 mm. diastolic on admission and remained at that level. The temperature was elevated on admission but was otherwise normal throughout the period of his hospital observation. There was no increase in his pulse or respiratory rate. Roentgenographic and fluoroscopic examinations of his heart were normal at all times. There was no leukocytosis, and the differential count remained normal. The red cell sedimentation rate was very rapid and remained rapid for four and one-half weeks. His basal metabolic rate was plus 2; blood Kahn and Wassermann reactions were negative; blood sugar 86 mg. per 100 c.c. of serum; blood cholesterol 194 mg. Tuberculin test was negative and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 250 units. Electrocardiograms (figure 2) taken 24 hours after onset of the substernal pain showed a slight RT elevation in Leads I and II and a marked RT_4 elevation and inverted T_2, T_3 and T_4. At the end of the third week the tracings showed a marked T inversion in Leads II and III with the picture of a characteristic posterior wall infarction. At the end of four months the pattern of all leads was approaching normal. There were no QRS changes at any time. The clinical course was uneventful.

Case 3. B. P. Patient was a 21 year old colored soldier, a farmer in civilian life, who had been in military service about two months. His family history was not contributory. He had suffered severe sore throats as a child, and for 13 years he was troubled with a chronic arthritic condition of the hands. There was nothing else pertinent in his past history. He denied any venereal infection. He never smoked. He was admitted to the hospital on November 5, 1942 with the story that for three weeks prior to admission he had suffered with severe sore throats. After admission to the hospital, he developed pains in his left hand, wrist and elbow, and he started complaining of precordial distress with exertion.

The only pertinent findings on physical examination were enlarged and inflamed tonsils and mild contractures of both hands. The heart was not enlarged and no pertinent adventitious sounds were heard. His blood pressure was 118 mm. Hg systolic and 70 mm. diastolic and remained at that level throughout his hospital stay. There was no temperature elevation and no increase in the pulse or respiration rate. There was no leukocytosis and his differential count remained normal. His red cell sedimentation rate was elevated for about 10 days. His basal metabolic rate was plus 4; blood Kahn and Wassermann reactions were negative; blood sugar 106 mg. per 100 c.c. of serum; blood cholesterol 215 mg. Tuberculin test was negative and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 350 units. Electrocardiograms (figure 3) taken three days after the onset of the precordial pain showed an inversion of T_2 and a diphasic T_3 with no RT changes. Serial studies over a period of three months showed a gradual return toward the normal pattern. There were no QRS changes at any time. The clinical course was uneventful. The contractures of both hands have persisted unchanged.

Case 4. J. A. L. Patient was a 25 year old white soldier, a hospital attendant as a civilian, who had been in military service 20 months. His family history was not contributory. He had suffered frequent sore throats as a child. There was noth-

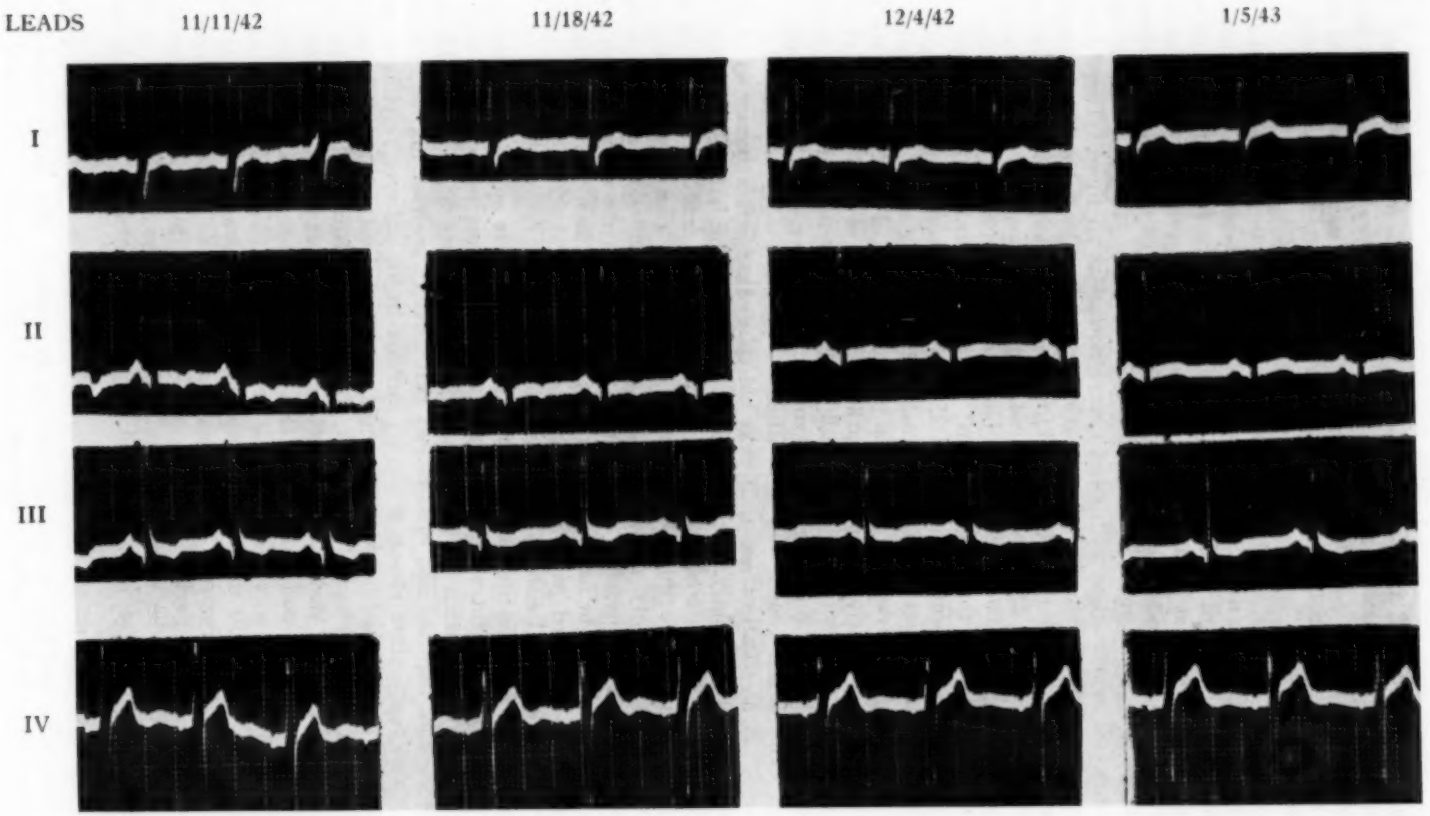
LEADS
11/11/42
11/18/42
12/4/42
1/5/43
I
II
III
IV

FIG. 3. Case 3.

LEADS
12/8/42
12/28/42
1/5/43

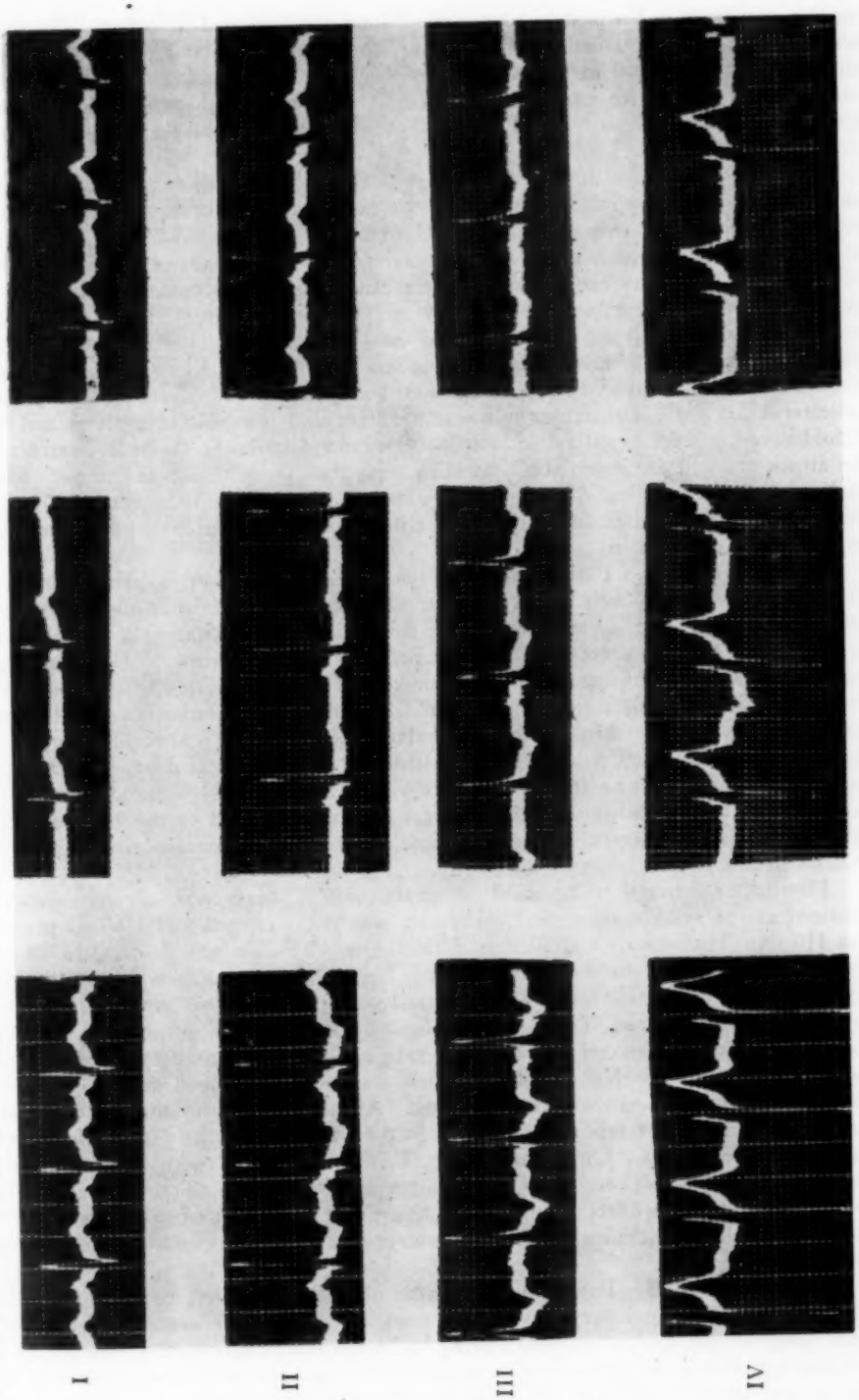

FIG. 4. Case 4

ing else pertinent in his past history. He denied any venereal infection. He was a heavy smoker. He had had an upper respiratory infection about two weeks before admission but continued at his work. On the night before admission, while doing routine ward duties, he experienced sudden sharp substernal pain which radiated down both arms. The pain lasted about 30 minutes and left him weak and perspiring profusely.

On physical examination his tonsils appeared chronically diseased, scarred, pitted and ragged. The examination was otherwise negative. His heart was not enlarged, and no adventitious sounds were heard. His blood pressure was 122 mm. Hg systolic and 60 mm. diastolic on admission and remained within that range through his hospital stay. There was no temperature elevation and no increase in his pulse or respiratory rate. There was no leukocytosis and his differential count remained normal. His red cell sedimentation rate was elevated and remained elevated for about four weeks. His basal metabolic rate was plus 4; blood Kahn and Wassermann reactions were negative; blood sugar was 80 mg. per 100 c.c. of serum; blood cholesterol 225 mg. Tuberculin test was negative and tests for brucellosis and coccidioidomycosis were negative. Electrocardiograms (figure 4) taken 24 hours after the attack showed an inverted T_2 and T_3 with no appreciable RT change. Serial studies showed a gradual return of the abnormal variations to normal. No QRS changes were observed at any time. The clinical course was uneventful. There was no recurrence of the pain.

Case 5. J. O. T. Patient was a 27 year old white officer, a lumber dealer in civilian life, who had been in military service six months. His family history was not contributory. He had suffered severe sore throats, necessitating a tonsillectomy, as a child. There was nothing else pertinent in his past history. He denied any venereal infection. He was a moderate smoker. He was admitted to the hospital on December 4, 1942, with a story that about four weeks before admission he had suffered with severe sore throats for a period of four days. Two weeks later he developed generalized stiff painful joints, which lasted for several days. Twenty-four hours before admission he developed severe vice-like pains over the precordium. The pain radiated to the elbows of both arms and was more marked on the left side. The pain would last for several hours at a time. He required repeated hypodermic injections of morphine to control the pain.

Physical examination revealed a pharyngitis. There was a transient soft localized apical systolic murmur. His heart was not enlarged. His blood pressure was 110 mm. Hg systolic and 80 mm. diastolic on admission and dropped to 90 mm. systolic and 70 mm. diastolic two days later. He ran a temperature of about 100.5° F. for about three days. He had a moderate tachycardia during this period. There was no cyanosis or dyspnea. There was no leukocytosis and his differential count remained normal. His red cell sedimentation rate was very rapid and remained rapid for about five weeks. His blood Kahn reaction was negative; blood sugar 80 mg. per 100 c.c. of serum; blood cholesterol 160 mg. An antistreptolysin titer determination showed 833 units. Electrocardiograms (figure 5) taken 24 hours after onset showed only an RT_2 elevation. On serial studies, T inversions developed characteristics of an anterior wall infarction. No QRS changes were observed. Tracings taken about two months after the onset showed a tendency of the pattern of all leads to revert back to normal. The clinical course was uneventful. There was no recurrence of the pain.

Case 6. P. W. B. Patient was a 28 year old colored soldier, a farmer in civilian life, who had been in military service four months. Two of his sisters had rheumatic heart disease. He gave a story of having had a rheumatic infection at the age of 10. He also suffered throat infections as a child. He had had an uncomplicated gonorrhea at the age of 15, which was treated and pronounced cured. He never smoked.

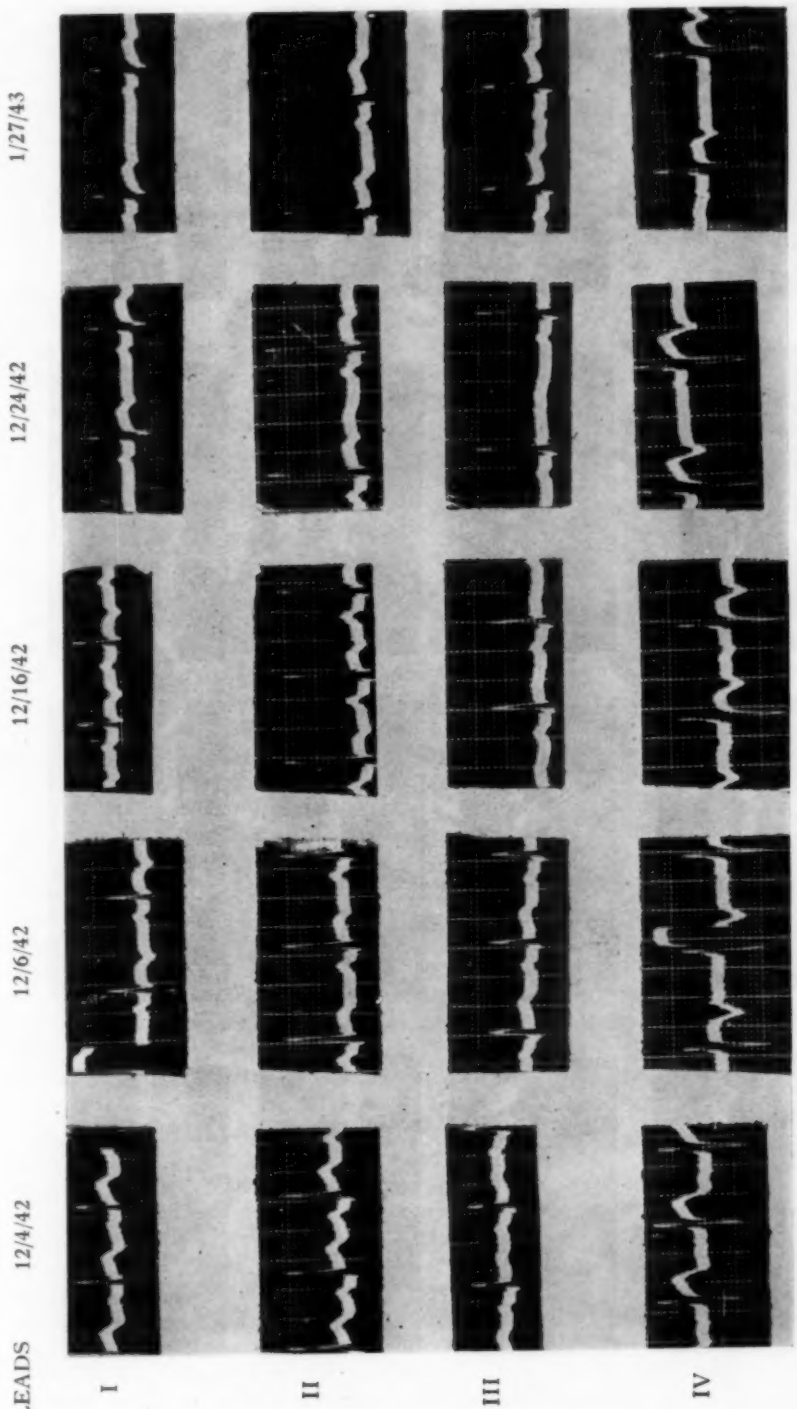

FIG. 5. Case 5.

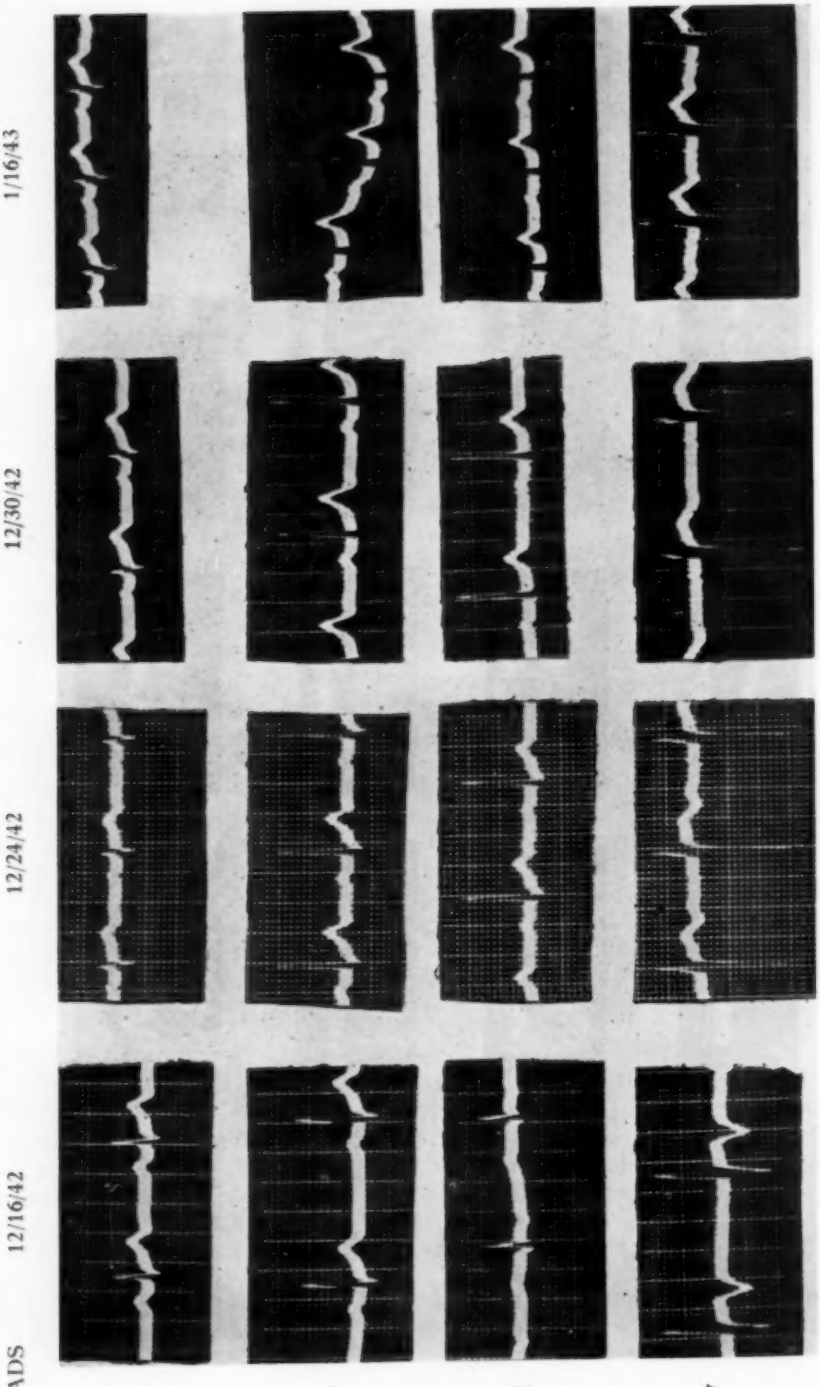

FIG. 6. Case 6.

For a period of about five years prior to his admission to the hospital, he had been suffering attacks of precordial pain. The pain radiated to the left shoulder, down the inner side of the left arm to the fingers. Attacks occurred with exertion and subsided with rest. About 10 days before admission he had an upper respiratory infection which lasted a few days. On the day before admission he had an attack of pain which lasted about 15 minutes and left him weak and perspiring.

Physical examination was entirely negative except for a moderate pharyngitis. The heart was not enlarged, and there were no abnormal sounds. His blood pressure was 150 mm. Hg systolic and 90 mm. diastolic on admission and ranged around 135 mm. systolic and 80 mm. diastolic during his hospital stay. There was no temperature elevation. There was no increase in the pulse or respiratory rate. There was no leukocytosis, and his differential count remained normal. His red cell sedimentation rate was moderately elevated for about two weeks. His basal metabolic rate was minus 2; blood Kahn and Wassermann reactions were negative; blood sugar was 96 mg. per 100 c.c. of serum; and blood cholesterol 166 mg. Tuberculin test was negative, and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 200 units. Electrocardiograms (figure 6) taken 48 hours after onset showed an inverted T_4 with no appreciable RT change. Serial studies showed the T_4 becoming diphasic and finally upright with a normal pattern. No QRS changes were observed at any time. He continued to have occasional mild anginal manifestations on effort. These were relieved by rest and also by nitroglycerine, 1/200 grain under the tongue. The clinical course was otherwise uneventful.

Case 7. D. S. The patient was a 33 year old white male, a truck driver in civilian life, who had been in military service three months. His family history was not contributory. He had had a tonsillectomy at the age of 21 because of severe sore throats. There was nothing else pertinent in his past history. He denied any venereal infection. He was a heavy smoker. He was admitted to the hospital on November 4, 1942, with a story that several weeks before admission he suffered a throat infection. For a week prior to admission, he noticed progressive dyspnea and gagging when hiking. The night before admission, while sitting quietly, he suddenly developed severe pain over the precordium. He vomited and collapsed. The pain lasted about half an hour.

Physical examination was entirely negative except for infected tonsillar tabs. The heart was not enlarged, and there were no adventitious sounds. His blood pressure was 120 mm. Hg systolic and 80 mm. diastolic on admission and remained within normal range. There was no temperature elevation and no increase in the pulse or respiratory rate. There was no leukocytosis, and his differential count remained normal. His red cell sedimentation rate was markedly elevated and remained elevated for about six weeks. His basal metabolic rate was plus 3; blood Kahn and Wassermann reactions were negative; blood sugar was 95 mg. per 100 c.c. of serum; and blood cholesterol, 195 mg. Tuberculin test was negative, and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 350 units. Electrocardiograms (figure 7) taken 24 hours after admission showed a slight RT elevation and a deeply inverted T_4. On serial study, there was a gradual return to normal in about eight weeks. No QRS changes were observed at any time. The clinical course was uneventful.

Case 8. E. K. The patient was a 36 year old colored soldier, a laborer in civilian life, who had been in military service four months. His family history was not contributory. He had had frequent sore throats as a child. There was nothing else pertinent in his past history. He denied any venereal infection. He was a light smoker. He was admitted to the hospital on December 7, 1942 with a story that he had been suffering with severe sore throats and hoarseness for a month. After his admission to the hospital, he developed joint disturbances, involving his left

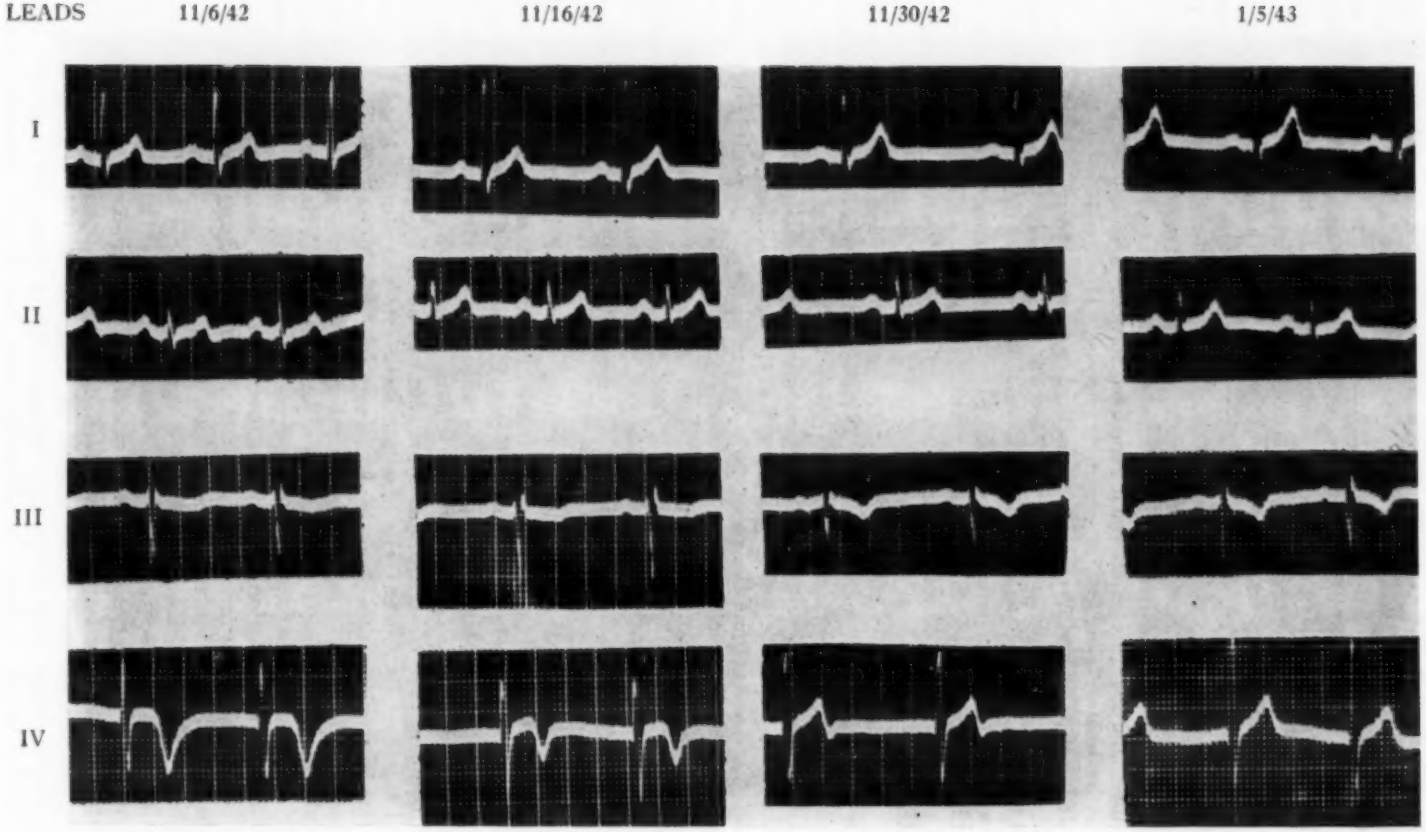

FIG. 7. Case 7.

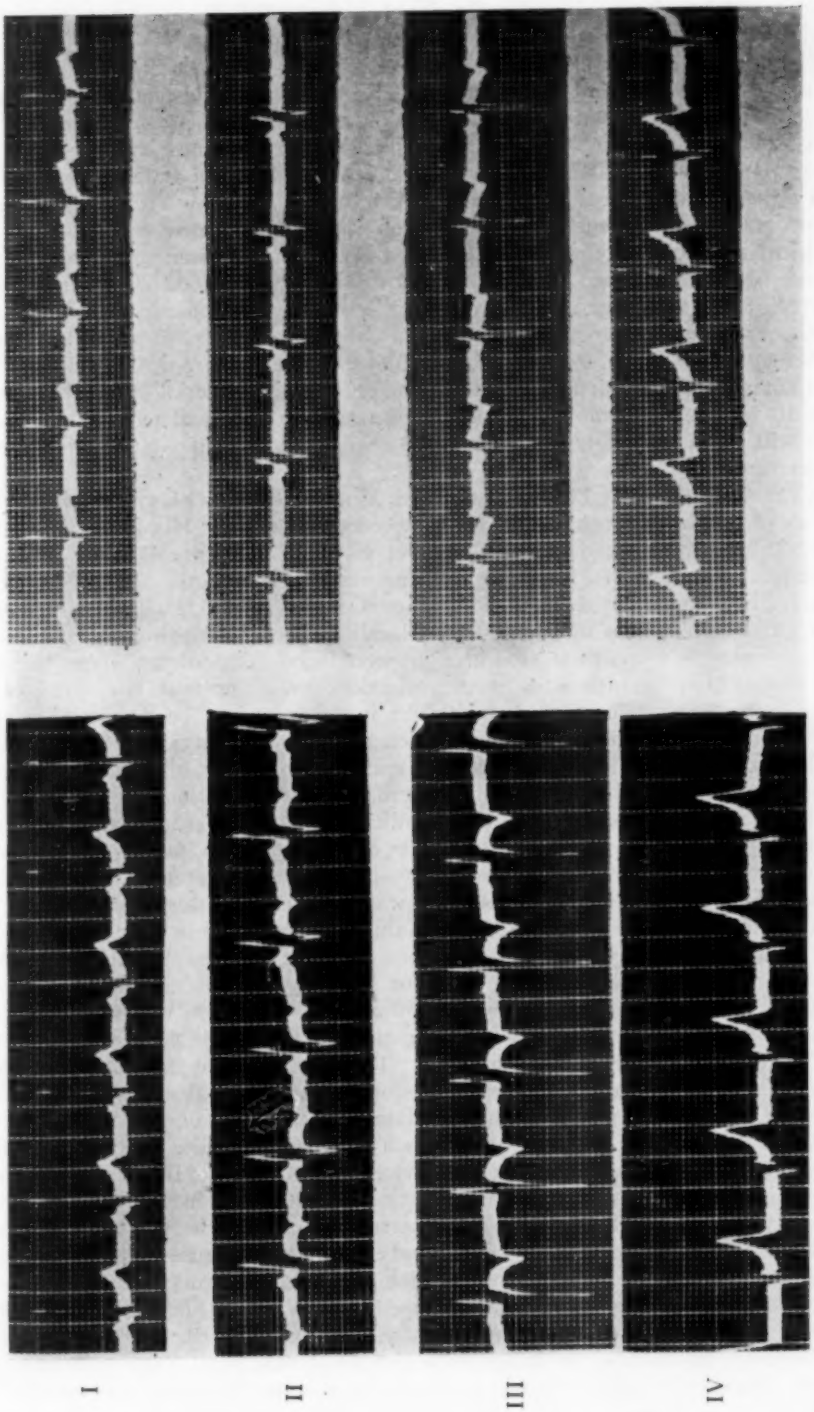

FIG. 8. Case 8.

shoulder and left knee. He also developed a precordial discomfort aggravated by exertion.

On physical examination, there was a pharyngitis. The heart was not enlarged, and no adventitious sounds were heard. The left knee and shoulder were painful on motion with no abnormal physical findings. His blood pressure was 112 mm. Hg systolic and 78 mm. diastolic on admission and remained at about that level during his hospital stay. There was no temperature elevation and no increase in the pulse or respiratory rate. There was no leukocytosis, and his differential count remained normal. His red cell sedimentation rate was elevated for about 10 days. His basal metabolic rate was plus 6; blood Kahn and Wassermann reactions were negative; blood sugar was 83 mg. per 100 c.c. of serum; blood cholesterol 192 mg. Tuberculin test was negative, and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 180 units. Electrocardiograms (figure 8) taken about 72 hours after the onset of precordial pain showed a slight coving and inversion of T_2 and an inverted T_3. On serial study at the end of about 10 weeks, there was a tendency for a return to a normal pattern. There was a left axis deviation but no pertinent QRS changes at any time. The clinical course was uneventful.

Case 9. J. L. W. The patient was a 37 year old colored soldier, a laborer in civilian life, who had been in military service three months. His family history was not contributory. He had suffered frequent sore throats as a child, and he had had pneumonia at the age of 33. He denied any venereal infection. He was a moderate smoker. He was admitted to the hospital on October 30, 1942, with a story that for many years he had been suffering from a localized precordial pain. It came on with exertion, was not sufficient to stop him but would slow him down. About two weeks before admission he suffered a throat infection for about four days. Three days before admission, while getting out of bed in the morning, he developed a severe, localized compressing precordial pain, which lasted several days.

Physical examination was entirely negative except for bilateral hypertrophied inflamed tonsils. The heart was not enlarged, and no adventitious sounds were heard. His blood pressure was 134 mm. Hg systolic and 82 mm. diastolic and remained at about that level. There was no temperature elevation and no increase in the pulse or respiratory rate. There was no leukocytosis, and his differential count remained normal. His red cell sedimentation rate was elevated for about three weeks. His basal metabolic rate was minus 3; blood Kahn and Wassermann reactions were negative; blood sugar was 83 mg. per 100 c.c. of serum; and blood cholesterol 200 mg. Tuberculin test was negative, and tests for brucellosis and coccidioidomycosis were negative. An antistreptolysin titer determination showed 166 units. Electrocardiograms (figure 9) taken four days after the onset of the attack showed an inverted T_2 and T_3 of low voltage and diphasic T_4. There were no appreciable RT changes. Serial studies showed a gradual return to normal pattern in about six weeks. There were no QRS changes at any time. The clinical course was uneventful.

Case 10. H. P. L. The patient was a 37 year old white soldier, a farmer in civilian life, who had been in military service three months. His family history was not contributory. There was nothing pertinent in his past history aside from sore throats as a child. He denied any venereal infection. He was a mild smoker. He was admitted to the hospital on November 24, 1942, because of a severe reaction to typhoid inoculation. On routine questioning he gave a story that about one year before admission to this hospital he developed a polyarthritis of fleeting character and fever. Three days later badly infected tonsils were removed. Ten days after the tonsillectomy, he suffered an attack of severe substernal pain. The pain radiated to the left shoulder and arm. He was confined to a hospital for about four months. The diagnosis of an acute coronary occlusion was made and confirmed by electrocardio-

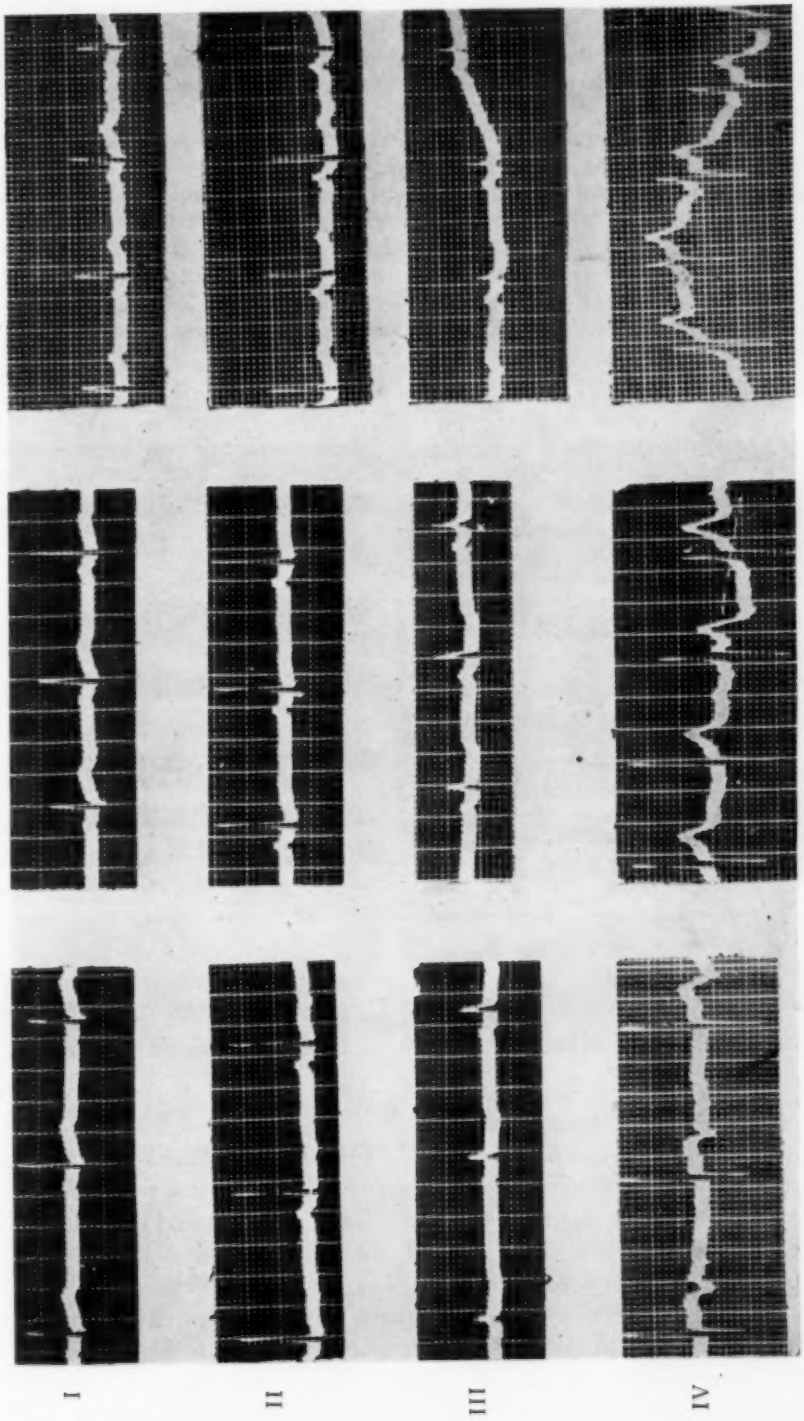

FIG. 9. Case 9.

graphic examination. He had a slight elevation of temperature of about 100.5° F. for several days. There was no leukocytosis, but a rapid red cell sedimentation rate. After a prolonged convalescence, he returned to farming until his induction into military service. At this time he had no symptoms referable to his cardiovascular system.

Physical examination at the time of the present hospital admission was entirely negative. The heart was not enlarged and responded normally to exercise. Chest roentgenogram was normal; blood count and red cell sedimentation rate were normal; urinalysis was normal. His basal metabolic rate was plus 4. Blood Kahn and Wassermann reactions were negative. Blood sugar was 104 mg. per 100 c.c. of serum; blood cholesterol 190 mg. Tuberculin test was negative. Electrocardiograms (figure 10) taken four days after the attack of the previous year showed a slight RT_2 and RT_3 depression and an inverted T_2 and T_3. Tracings taken almost one year later were entirely normal.

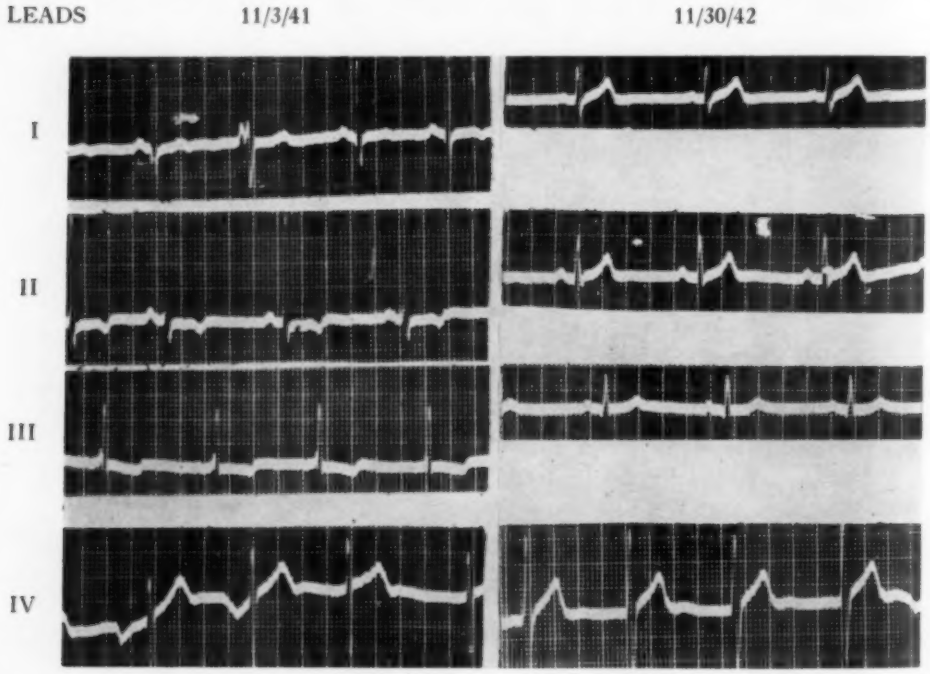

FIG. 10. Case 10.

Analysis of the Case Reports (table 1). It is observed that the ages of the patients ranged between 20 and 37. Six of the 10 were under 30, and the average age of the entire group was 28.4 years. Six of the 10 cases were negroes.

The family history was not contributory except in case 6, where two sisters are supposed to have had rheumatic fever. The patient gave a story that he, too, had rheumatic fever at the age of 10, although no evidence of valvular heart disease was evident during the period that we observed him. All the cases gave histories of severe throat infections during childhood.

CHART I

No.	Age	Race	F.H.	Past History		To-bacco	History of Attack				Physical and Laboratory Findings							Electrocardiograms				
				T.I.	A.P.		U.R.I.	J.P.	Card. Pain	Col-lapse	U.R.I.	Card. Find.	Fever	Leuk.	Rapid S. Rate	Bl. Chol.	Anti-strepto-lysin Titer	QRS Ch.	RT Ch.	T Changes		EKG Rec.
																				Ant.	W. Post	
1	20	Col.	N.C.	x	x	0	x		xxx	x	x	Slt. E. TSM		0	x	215	250 U	0	x		x	
2	20	Col.	N.C.	x		xxx	x		xxx		x			0	x	194	250 U	0	x		x	x
3	21	Col.	N.C.	x		0	x	x	xx	x	x			0	x	215	350 U	0			x	
4	25	Wht.	N.C.	x		xxx	x		xxx		x			0	x	225		0			x	x
5	27	Wht.	N.C.	x		xx	x	x	xxx		x	TSM	100.5 3 da	0	x	160	833 U	0	x	x		
6	28	Col.	R.F.	R.F. x	x	0	x		xxx		x			0	x	153	200 U	0		x		x
7	33	Wht.	N.C.	x		xxx	x		xxx	x	x			0	x	195	350 U	0	x	x		x
8	36	Col.	N.C.	x		x	x	x	xx		x			0	x	192	180 U	0			x	
9	37	Col.	N.C.	x	x	xx	x		xx		x			0	x	200	166 U	0		x		x
10	37	Wht.	N.C.	x		x	x	x	xxx	x			100.5 4 da	0	x	190		0			x	x

Tuberculin tests, tests for brucellosis, and coccidioidomycosis were negative in all cases. Blood sugar determinations were normal in all cases. Basal metabolic rates were within normal range in all cases. Blood Kahn and Wassermann reactions were negative in all cases.

N.C.—Not Contributory
R.F.—Rheumatic Fever
T.I.—Throat Infections
T.S.M.—Transient Systolic Murmur
A.P.—Angina Pectoris
U.R.I.—Upper Respiratory Infections
J.P.—Joint Pains

Three of the cases were heavy smokers, two more moderate smokers, two mild smokers and three cases did not smoke at all. No relationship of the use of tobacco to the disease can be drawn from these figures.

In all of the cases a respiratory infection preceded the cardiac attack by a period of several days to four weeks. In four of the cases there were associated joint disturbances.

The attacks were characterized by only moderate precordial pain in four of the 10 cases. The remaining six cases were characterized by severe precordial pain, and in four of these there was associated collapse. Three of the 10 cases, including case 1, age 20, gave a story of having suffered an angina of effort dating back five years or more, which would mean that case 1 started complaining of angina pectoris at the age of 15.

On physical examination, nine of the 10 cases had evidence of throat inflammation. Cardiac findings were negligible. Only case 1 showed evidence of slight enlargement of the heart to the left, both on physical examination and by chest roentgenogram. Two of the cases had transient apical systolic murmurs. Cases 5 and 10 had a low grade fever and a moderate tachycardia for three or four days at the onset.

There was no leukocytosis in any case, but all had rapid red cell sedimentation rate determinations. Blood cholesterol figures were within normal limits or only slightly elevated. Blood sugars were normal, basal metabolic rates were within normal limits. Tuberculin tests and tests for brucellosis and coccidioidomycosis were negative in all cases. Blood Kahn and Wassermann reactions were negative in all cases.

Antistreptolysin titers were obtained in eight of the 10 cases. In five, the figures were high enough to implicate the hemolytic streptococcus. There is a question as to how much reliance can be placed on the significance of the negative results in the remaining three cases, since the titer determinations were made two to three months after the acute respiratory episode had subsided in these cases.

An analysis of the electrocardiographic variations shows that there were no appreciable QRS changes in any case. Four cases showed RT changes; but all showed T changes, which indicated posterior wall localization in six cases and anterior wall localization in four. In six of the 10 cases the electrocardiographic patterns reverted to normal. In three of the cases there was a partial return. Only in case 1 did the changes appear to be permanent. This was the 20 year old patient who had suffered angina pectoris since the age of 15.

Discussion

In all the cases, the clinical picture, course and electrocardiographic variations were suggestive of an unusual type of cardiac infarction. Most authors are in general agreement that cardiac infarction, secondary to a coronary occlusion on a coronary sclerotic basis, occurs most commonly over the age of 40, infrequently between the ages of 30 and 40, and very rarely under 30. Levine [1] reports only three instances between the ages of 30 and 39 in a total of 145 consecutive cases. There is also general agreement that

the occurrence is relatively uncommon in the negro as compared to the white race. In this series of cases, 60 per cent are between the ages of 20 and 28 and 60 per cent are in negroes. The ratio of negro to white troops at this camp during this period was comparatively small.

The high incidence of throat infections in the past history, the common onset of the cardiac manifestations following respiratory infections, usually sore throats, and in four instances the presence in addition of joint disturbances are highly suggestive of an infectious basis for the disease picture.

Three of the cases with the same history of throat infections, similar clinical picture, course and characteristic electrocardiographic variations had, in addition, a long history of angina, typically vascular in type. These three cases seem to fall into a separate group under the same heading. Associating the two groups it is logical to assume a vascular basis for the disease. In both groups we can assume recent vascular lesions and in the second group, in addition, preëxisting vascular changes.

It is widely accepted that rheumatic fever is closely associated with hemolytic streptococcus infections. Five of the eight cases of our series, on whom antistreptolysin titers were determined, showed figures high enough to be significant, with a plausible reason as to why they were not high in the remaining three. Coburn [2] found that the titer, as a rule, remains high as long as the disease remains active.

Jones and Mote [3] found that 58 per cent of the initial rheumatic attacks were preceded by infections of the upper respiratory tract, and that in 271 observed recurrent attacks, 67 per cent were associated with infections of the respiratory tract, two-thirds of which were manifested by sore throat.

Arterial changes occurring in rheumatic fever were discussed by French authors as far back as 1870 (Hayem,[4] Martin,[5] Landouzy and Siredey,[6, 7] and Huguenin [8]). Von Glahn and Pappenheimer [9] in 1926 accurately described the peripheral vascular changes according to our present conception, and Karsner and Bayless [10] thoroughly studied lesions of the coronary arteries in rheumatic infections. They speak of inflammatory and fibrotic lesions of the coronary arteries and mention that fibrinoid degeneration with the formation of a fibrin-like material is particularly suggestive but not diagnostic. Boyd [11] writing on this point remarks "the most important lesion is an intimal fibrosis of the coronary vessels in early life thus producing precocious coronary sclerosis with narrowing of the lumen, which may cause severe myocardial damage. The abundant myocardial scarring with progressive myocardial disability is better accounted for by coronary narrowing than in any other way." Back in 1906, Aschoff [12] speaking on this subject said: "Healing of the arteritis and periarteritic foci can cause such sclerotic narrowing that ischemic necrosis may result," and he says further "at all events we believe that all scars are due either to plugging of vessels or anemic necrosis and not primarily to interstitial myocarditis."

Acute coronary occlusions occurring in the course of acute rheumatic fever were reported by Kaufmann [13] in 1922, Monckeberg [14] in 1924, and Slater [15] in 1930. There have been a number of cases reported since.

The question has been raised, if we assume a rheumatic basis for the disease in this series of cases, how can the absence of rheumatic valvular disease in all the cases be explained? Hall and Anderson [16] in a recent publication investigated the presence of the so-called rheumatic stigmata in hearts that were free of gross deforming valvular lesions. Using 12 specimens with gross valvular lesions showing all the stigmata in abundance as controls, they studied 112 hearts free of gross valvular lesions and in 90 per cent found rheumatic stigmata. Vascular stigmata were frequently observed. Interesting were their observations relative to the acute vascular changes showing stages of fibrin infiltration and necrosis and the old or chronic stage with hyalinized fibrous wall. They concurred in the belief that the lesions were the result of allergic-hyperergic responses to recurrent upper respiratory infections with the rheumatic virus in persons who are relatively immune. They felt that the hemolytic streptococcus would seem logically to fit the rôle of the rheumatic agent.

Similar lesions have been observed in infections with other streptococcal strains, and Vaubel [17] and later Hemken [18] experimentally produced coronary arteritis with intravenous injections of horse serum. Hall and Anderson [16] emphasized that it is not necessary to demonstrate a specific organism to invoke the allergic hypothesis. They feel that the rheumatic stigmata they demonstrated represented manifestations of allergy to repeated upper respiratory infections with a rheumatic virus.

Summary

1. Ten cases presenting cardiac manifestations and characteristic electrocardiographic variations suggestive of an unusual type of cardiac infarction are presented.

2. The cases ranged in age between 20 and 37, the average being 28.4 years; 60 per cent of the group were negroes.

3. All cases gave a history of upper respiratory infections; four of the cases had joint disturbances; five of eight of the cases had high antistreptolysin titers. None of the cases had leukocytosis or polynucleosis, but all had rapid red cell sedimentation rates.

4. The electrocardiographic variations were characterized by T changes with both anterior and posterior wall type of localization, occasional RT changes, and the consistent absence of QRS abnormalities.

5. All the cases improved clinically. The electrocardiograms reverted to a normal pattern in six of the cases and in three the changes improved considerably with the probability that they would in time revert to normal.

6. The upper respiratory infections, the occasional joint disturbances, and the high antistreptolysin titers suggest a rheumatic type of infection.

7. There is general agreement on the occurrence of coronary arteritis in rheumatic infections. Acute inflammatory arteritis characterized by fibrinoid degeneration and late fibrotic changes has been demonstrated. Cases of our series fit into both types clinically.

Conclusions

1. The relationship of the upper respiratory infections, occasional joint disturbances and high antistreptolysin titers to the clinical picture and the consistent characteristic electrocardiographic variations suggest a rheumatic or some correlated type of arteritis as the basis for the pathologic lesion in these cases.

2. This study further suggests the possibility that many cases of coronary disease of later life have as their basis an infectious arteritis dating back to their youth.

I wish to express my appreciation to Colonel Arthur R. Gaines, Commanding Officer of Station Hospital, Fort Ord, California, for his assistance and coöperation in preparation of this paper.

BIBLIOGRAPHY

1. Levine, Samuel A.: Coronary thrombosis, Medicine, 1929, viii, 245.
2. Coburn, A. F.: Faulty disposal of *Streptococcus hemolyticus* in relation to the development of rheumatic lesions, Trans. and Stud. Coll. Phys. Philadelphia (4th Series), 1940, viii, 91.
3. Jones, T. D., and Mote, J. R.: The clinical importance of infection of the respiratory tract in rheumatic fever, Jr. Am. Med. Assoc., 1939, cxiii, 898.
4. Hayem, G.: Recherches sur les rapports existant entre la morte subite, Arch. de physiol. norm. et path., 1869, ii, 699.
5. Martin, H.: Des lesions viscerales consecutives a l'endarterite obliterante et progressive, Rev. de méd., 1881, i, 369.
6. Landouzy, L., and Siredey, A.: Contribution à l'histoire de l'arterite typhoidique, Ibid., 1885, v, 843.
7. Landouzy, L., and Siredey, A.: Etude des localisations angio-carideques typoidaques, Ibid., 1887, vii, 919.
8. Huguenin, P.: Myocardite infectieuse diphtherique, Ibid., 1883, viii, 999.
9. von Glahn, William C., and Pappenheimer, Alwin M.: Specific lesions of peripheral blood vessels in rheumatism, Am. Jr. Path., 1926, ii, 235.
10. Karsner, Howard T., and Bayless, Frances: Coronary arteries in rheumatic fever, Am. Heart Jr., 1934, ix, 557.
11. Boyd, W.: Pathology of internal diseases, 2nd ed., 1936, Lea and Febiger, Philadelphia.
12. Aschoff, L.: Die leutige Lehre von der pathologischanatomischen Grundlagen der Herzschwäche, 1906, G. Fischer, Jena.
13. Kaufmann: Spezielle pathologische Anatomie, 1922, 1, 42, 7th and 8th Auflage, Berlin u. Leipzig.
14. Monckeberg, J. G.: Handbuch d. speziellen pathologischen Anatomie u. Histologie, 1924, Julius Springer, Berlin, ii, 391.
15. Slater, S. R.: The involvement of the coronary arteries in rheumatic fever, Am. Jr. Med. Sci., 1930, i, 22.
16. Hall, E. M., and Anderson, L. R.: The incidence of rheumatic stigmas in hearts which are usually considered non-rheumatic, Am. Heart Jr., 1943, i, 64.
17. Vaubel, E.: Die Eiweissüberempfindlichkeit (Gewebshyperergie) des Bindegewebes (II Teil.) Experimentelle Untersuchungen zur Erzeugung des rheumatischen Gewebsschadens im Herzen und in den Gelenken, Beitr. z. path. Anat. u. z. allg. Path., 1932, lxxxix, 374.
18. Hemken, L.: Allergy, lesions produced by injection of protein. Read before the Pathology and Bacteriology Section of the California Medical Association at the Sixty-Fifth Annual Session, Coronado, May 25–28, 1936. (Quoted by Hall and Anderson.[16])

SYPHILIS AND DIABETES MELLITUS; A LONG-TERM CLINICAL STUDY *

By Frank S. Perkin, M.D., F.A.C.P., *Detroit, Michigan*

The rôle of syphilis in the etiology of diabetes mellitus has long been a subject of controversy. Isolated cases of the association of the two diseases have appeared in the literature since 1889; some reported apparent improvement in the diabetes following antisyphilitic treatment, whereas others noted a loss of carbohydrate tolerance. The majority of the reports have appeared in the foreign literature where the subject has aroused more interest.

These cases were all subject to the just criticisms that they had not been properly studied from a diabetic standpoint, they had not been observed for an adequate period, and were insufficient in number to justify definite conclusions.

The first case which was properly studied was that of Paullin and Bowcock [1] in 1924. A definite improvement in the diabetic status following antisyphilitic treatment was demonstrated by glucose tolerance tests and clinical improvement. Unfortunately, this patient died several years later of other causes.

The natural result of the lack of information on such an important subject has been a wide variation of opinion. Lemann [2, 3] felt there was evidence that diabetes in some cases was produced by syphilitic disease of the pancreas, but he believed it was very rare. Recently two extensive studies have appeared which might seem to have closed the subject.

Williams [4] treated 17 cases of syphilis in a group of 1,000 diabetics without finding any evidence of improvement on careful study of their diabetes. In an effort to eliminate all doubtful cases of syphilis, he treated only cases showing other definite clinical evidence of syphilis as well as positive serologic reactions. It is my belief that he thus eliminated the group which is of most importance, i.e., the tertiary and latent syphilitic without other evidence of syphilis. His statement that severe diabetics with low carbohydrate tolerance requiring large doses of insulin frequently show subpositive Wassermann reactions with one or more antigens has not been verified in my experience or that of other observers. His findings thus would merely verify those of other students that in no cases of early or active syphilis was there any effect on the diabetes from anti-syphilitic treatment.

McDaniel, Marks and Joslin [5] have made a very complete statistical study of 258 cases of syphilis found in Joslin's group of 15,095 diabetic patients. There is included a very complete review of the literature and statistical data to which students of the subject may refer, and which make repetition unnecessary. From their analysis of this series, they were unable to find a

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From the Diabetic Service, Receiving Hospital, Detroit, Michigan.

single instance of cure of diabetes brought about by optimum anti-syphilitic treatment. Of interest was their conclusion that, theoretically, if "syphilitic diabetes" occurs, it would most likely be a late manifestation of syphilis occurring in older persons.

In the belief that the controversial opinions on the rôle of syphilis in diabetes were the result of lack of evidence based on prolonged observation and sufficient material, in 1928 a study of the problem was initiated. This was stimulated by the discovery of several cases of association of the two diseases which exhibited apparently an unusual improvement in their diabetic status while on antisyphilitic treatment. At Receiving Hospital, Detroit, there was an exceptional opportunity for such an investigation, with a large volume of diabetic patients from a section of society in which syphilis is unusually common. Also, these patients, because they received free treatment and insulin, were under observation for extended periods.

This report is based on personal observation in the majority of cases, and study of the records in the remainder, of all diabetics, 644 in number, attending Receiving Hospital and seen in private practice between 1928 and 1933, with a follow-up study in the succeeding years of such cases of interest as could be induced to continue under study and treatment.

This series is represented by the following statistics.

TABLE I

Total cases of diabetes	644	
No syphilitic serologic tests	94	
Cases included in this series	550	
Cases with positive syphilitic serologic tests	42	7.6%
Cases with positive history but negative serologic tests	12	2.2%
Total cases of possible syphilis	54	9.8%

The 94 cases without serologic tests represent cases which were hospitalized for very short periods, deaths shortly after admission, negligence in completing the examination, and various other causes. These cases were eliminated from consideration in the analysis.

The 42 definite and 12 probable cases represented the group in which anti-syphilitic therapy might prove to be of value.

TABLE II

Total cases in this series—550

	Syphilitic Group	Non-Syphilitic Group
Colored— 88	20—23%	68—77%
White—462	34— 7.4%	428—92.6%
Males—251	23— 9%	228—91%
Females—299	31—10.4%	268—89.6%

The colored cases constituted 37 per cent of the syphilitic diabetics and 14 per cent of the non-syphilitic diabetics. This only serves to demonstrate the greater incidence of syphilis in the colored race and has no definite bear-

ing on the present problem. The 9.8 per cent of our total diabetic cases with a syphilitic history closely conforms to the percentage in all Receiving Hospital admissions, and this might be taken as evidence against any etiological relation between syphilis and diabetes. On the other hand, it is to be considered that many hospital admissions are the result of conditions which are recognized as later manifestations of syphilis. Thus, the percentage of syphilitics in all cases of heart disease also is not greatly at variance with the percentage in all admissions. I do not believe that this method of analysis can be depended upon to give reliable evidence.

The distribution of cases between male and female is about even. This is at variance with the findings in McDaniel's [5] analysis of Joslin's series, but probably has no marked significance. However, it has been my impression that if syphilis is of significance in the diabetic, it is more likely to be in the diabetic female.

TABLE III

Age Groups

	1 to 30	30 to 40	40 to 50	50 to 60	60 and over
Non-Syphilitic Group....	10.5%	18.5%	20%	27.7%	24%
Syphilitic Group.....	2.3%	14.5%	35%	30.0%	17.5%

A very interesting observation is found in the study of the classification by age groups. The non-syphilitic group conforms to the usual findings in any series. The syphilitic group is concentrated in the later decades of life. Of the two cases under 30 years of age one was a known diabetic before contracting syphilis.

TABLE IV

Degree of Severity of Diabetes

	Mild	Moderate	Severe
Non-Syphilitic.....	131—26%	280—57%	85—17%
Syphilitic.....	30—55.5%	18—33.5%	6—11%

For purposes of classification, a mild diabetic was considered a case which did not require insulin on a maintenance diet, a moderate diabetic one who did not require more than 20 units of insulin daily, and a severe diabetic, one requiring more than 20 units of insulin daily. Although admittedly this is not an exact method, it affords figures for comparison. The syphilitic group is remarkable for the preponderance of mild cases, and severe cases in this group include one case that was known to have contracted his syphilis while diabetic. Because of the mildness of their diabetes and lack of symptoms, it was, as a rule, difficult to persuade these patients to continue a long course of treatment, and many after a short period would not return, stating they felt perfectly well.

In Joslin's series, based on a slightly different classification, 65.9 per cent were mild, 19 per cent moderate, and 8.9 per cent severe. The figures for the whole group are not given. In the present series the variation in severity of the diabetes between the non-syphilitic and syphilitic groups would appear to hold some possible significance.

TABLE V

Other Pathologic Lesions Resulting from Syphilis

	Cases
A. Central nervous system involvement	5
B. Cardiovascular involvement	1
C. Skin involvement	1

Few of these cases showed other pathologic lesions as a result of their syphilis.

This is in accord with the usual findings in tertiary syphilis. In view of the number found to have central nervous system involvement, spinal fluid studies should have been done in a larger percentage of cases.

TABLE VI

Response to Treatment

Cases in syphilitic group given antisyphilitic treatment	19
Cases showing varying degrees of improvement in tolerance following antisyphilitic treatment	14
Cases showing no improvement in tolerance following antisyphilitic treatment	5

The comparatively small percentage of cases which are included in the above summary is the result of including only those cases which were judged possibly to fall in the group where the association of the two diseases might be significant and which were treated and observed over an extended period. The cases in which no change in diabetic status occurred after adequate antisyphilitic therapy were regarded as cases in which the association of syphilis and diabetes was merely incidental. Some of the cases in which changes occurred will be described as giving possible evidence in the problem of etiological relationship.

Case 102. M.S., female, white, aged 54, weight 134 lbs., was first seen in February, 1929. She had been a known diabetic for over two years and was under treatment at the North End Clinic, where she had been on a diet and 15 units of insulin for several months. Her past history included typhoid fever in 1917. There was no family history of diabetes. She was admitted to Receiving Hospital for observation and discharged on a diet of CH. 90, P. 50, F. 140, with 10 units of insulin daily. She had been found to have positive Kahn and Wassermann reactions. Her glucose tolerance test at this time is shown in figure 1. She commenced antisyphilitic treatment and was given one course of arsenicals at the Board of Health. Following this she was treated at our clinic for a year with iodides, bismuth, and a further course of arsenicals.

In August, 1929, she was having occasional insulin reactions although not following her diet, and the insulin dosage was reduced to 5 units daily. In December, 1929, insulin was discontinued. The Wassermann reaction at this time was negative. A glucose tolerance test in February, 1930, was regarded as normal. From this time until 1935, she was without clinical or laboratory evidence of diabetes. Early in 1935,

she commenced to show abnormally high blood sugar readings and a tolerance curve in February, 1936, demonstrated a diabetes more severe than at any time during our observation. Kahn reaction at this time was negative. In December, 1941, she was still a severe diabetic, requiring 40 units of of protamine zinc insulin and 10 units of regular insulin daily for control.

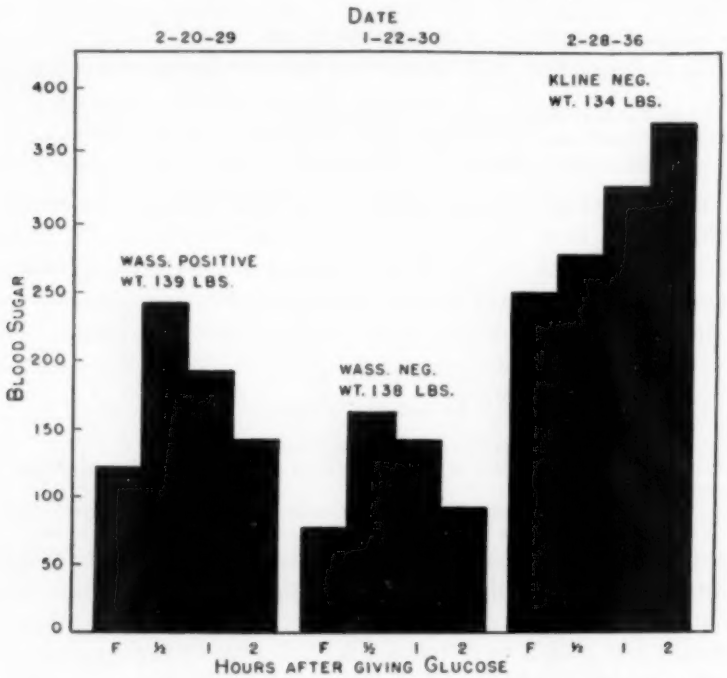

FIG. 1. M. S., female, aged 54 years, height 5′ 1″, standard weight 134 pounds, duration of diabetes 2½ years.

In this case there was demonstrated an improvement in the glucose tolerance to a point which might be regarded as non-diabetic, which it was difficult to ascribe to other causes than the antisyphilitic therapy. This improvement persisted for about five years, when the diabetes again became manifest and in a more severe degree, although the serologic tests for syphilis remained negative. None of the other so-called etiological factors could be demonstrated.

Case 356. J. W., female, colored, aged 40, weight 156, was first seen November, 1930. She had been told she had diabetes four months before, and her diabetes had not been controlled by a diet. There was no family history of diabetes. Her past history was unimportant except for one miscarriage and two stillbirths. Physical examination was negative with no clinical signs of syphilis. The Wassermann reaction was positive.

She was hospitalized for observation and discharged on a diet of CH. 90, P. 60, F. 120, with 20 units of insulin daily. The glucose tolerance test at this time is shown in figure 2. She was given antisyphilitic treatment consisting of bismuth, iodides, and one course of arsenical over a period of nine months, during which insulin was grad-

ually discontinued, although the patient was not following her diet. Following this she was seen at long intervals, showing normal blood sugar readings and no evidence of diabetes. Her Wassermann reaction was negative, and no further antisyphilitic treatment was given. In January, 1936, she commenced to show higher blood sugar levels, and complained of pain in the upper abdomen. On a diet of CH. 120, P. 70, F. 130, she required 5 units of insulin daily. Examination showed some liver enlargement, more marked in the left lobe. Gastrointestinal series showed no disease, and a glucose tolerance test gave a curve indicative of mild diabetes, although much better than five years previously. Her Kline reaction was positive, Kahn doubtful and

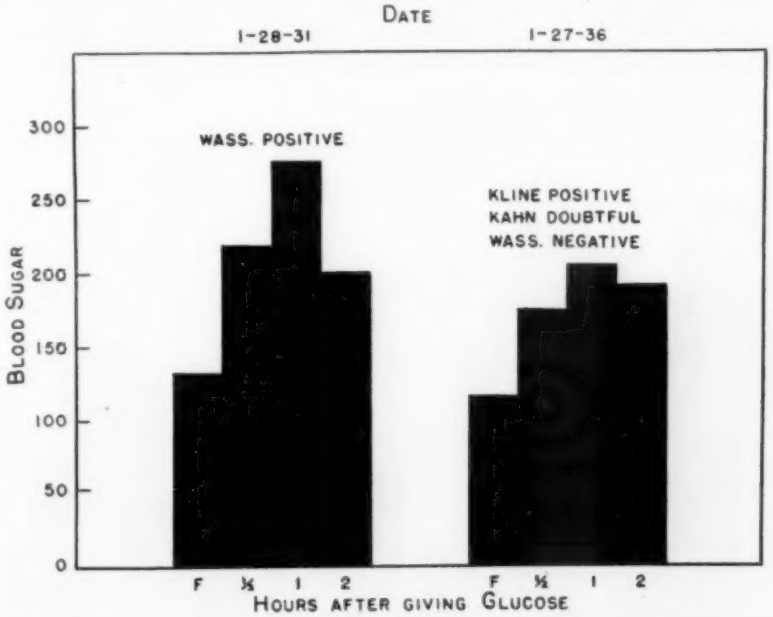

FIG. 2. J. W., female, aged 40 years, height 5′ 3″, standard weight 156 pounds, duration of diabetes 6 weeks.

Wassermann negative. In September, 1936, there was some persistence of upper abdominal pain. Gall-bladder roentgenograms showed no visualization following dye administration. She improved on medical treatment but required 15 units of insulin daily. There was no apparent response to further antisyphilitic treatment, either on the part of her diabetes or liver enlargement. Operation for possible gall-bladder disease was refused. In April, 1939, gall-bladder roentgenogram still showed non-visualization. In December, 1941, she was well controlled on 10 units of protamine zinc insulin daily.

This case showed an unusual improvement in the severity of her diabetes while on antisyphilitic treatment. The increase in severity some years later was associated with evidence of liver damage and a non-visualizing gall-bladder. The serologic tests for syphilis showed subpositive responses to some antigens. The lack of response to antisyphilitic therapy, however, suggests that some other etiological factor was now present, possibly a chronic cholecystitis.

Case 604. A. J., male, white, aged 49, weight 156, was first seen June, 1932. He had been rejected for life insurance one week previously following a glucose tolerance test. Important points in his history were a chancre 30 years before with one short course of treatment only, and the fact that his wife had numerous miscarriages before bearing living children. There was no family history of diabetes. His physical examination was essentially negative with no clinical manifestations of syphilis. The fasting blood sugar was 208 mg. A glucose tolerance test showed a definitely diabetic type of curve. His first Kahn reaction was negative. Following provocative treatment with iodides and arsenicals, one of two Kahn reactions was reported as positive. He was not placed on a diet and was given antisyphilitic treatment, iodides, bismuth, and a short course of arsenicals until December, 1932, when a glucose tolerance test gave a normal type of curve. Blood sugar levels were consistently normal. Treatment was continued until August, 1933, during which period there were no abnormal

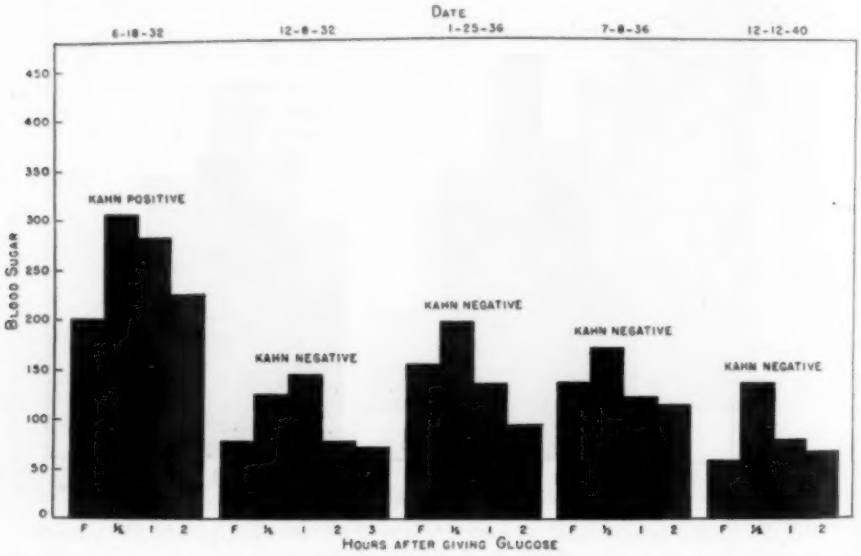

FIG. 3. A. J., male, aged 49, height 6′, standard weight 163 pounds, duration of diabetes unknown.

blood sugar levels, despite the fact that he had refused to accept welfare assistance and was living largely on bread and potatoes. He was seen at intervals until January, 1936, when he again showed a slight glycosuria, and a glucose tolerance test showed a mildly diabetic curve. He was given a further course of bismuth injections, continuing on an unrestricted diet. A curve in July, 1936, suggests a possible effect from this treatment. He was seen on rare occasions until December, 1940, when an unquestionably normal type of curve was obtained on a glucose tolerance test. Variations in weight from 1932 to 1940 never exceeded five pounds. In December, 1941, the blood sugar, after a high carbohydrate meal, was 82 mg.

This case in most series would be regarded as showing inadequate evidence of syphilis, yet if he had shown an aneurysm, for instance, its syphilitic origin would not have been doubted. It is difficult to explain this improvement on any other basis than that of his antisyphilitic therapy, as he received

no diabetic treatment, either diet or insulin. He is also one of the rare cases in which the diabetes is not manifest after a 10 year period, although experience with other cases suggests that it might recur at any time.

Case 127. A. W., female, white, aged 50, is perhaps the most interesting and instructive case. She was first seen in April, 1928, weight 270 pounds, a known diabetic for five years, poorly controlled but never had received insulin. Her past illnesses and family history were not of note. Her physical examination, except for her marked obesity and a ventral hernia, showed no significant findings. Her fasting blood sugar varied between 150 and 200 mg. She had positive Wassermann and Kahn reactions. She was placed on a low carbohydrate diet of CH. 60, P. 75, F. 125, similar to diets that she had presumably been following for several years. No insulin was given and antisyphilitic therapy was instituted. She received two courses of neo-

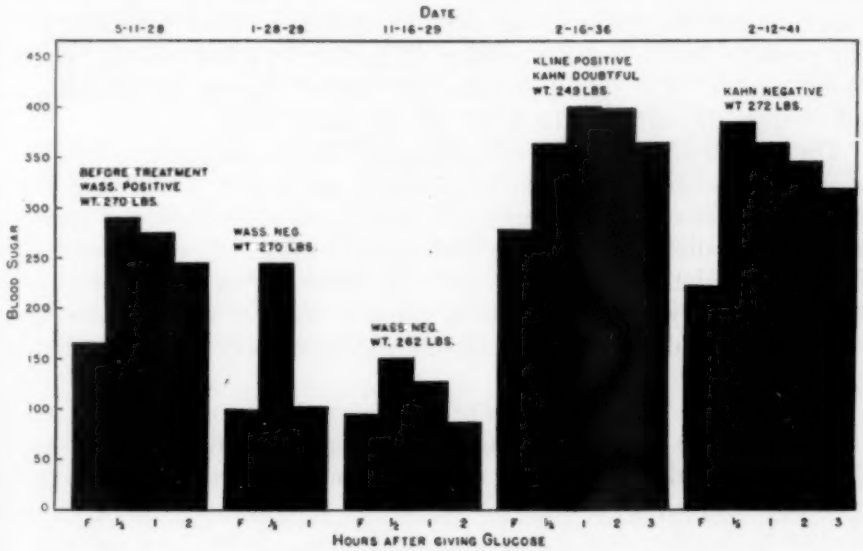

FIG. 4. A. W., female, aged 50, height 5′ 6″, standard weight 260 pounds, duration of diabetes 5 years.

salvarsan and continuous bismuth injections over a period. She slowly lost weight until in January, 1929, she weighed 252 pounds. Her Wassermann reaction was negative, and she was definitely improved from a diabetic standpoint. At this time she discontinued following a diet, and antisyphilitic therapy was continued in the form of bismuth intramuscularly and iodides. In November, 1929, she had gained to 262 pounds, was not on a diet or receiving insulin and was apparently non-diabetic to all tests. She was seen at intervals over the next few years, with at all times a normal fasting blood sugar. During this time she was confined to another hospital for her ventral hernia, where after tolerance tests, she was told she was non-diabetic.

She was lost to my observation for several years, but in 1934 returned to our clinic with a definite return of her diabetes. It is of interest to note that at this time she showed a positive Kline reaction and negative Kahn and Wassermann reactions. Her diabetes slowly increased in severity, and in 1935 she was placed on insulin. In October, 1935, she showed a positive Kline and a doubtful Kahn reaction. In February, 1936, the severity of her diabetes as evidenced by a glucose tolerance curve

was greater than at any time during our observation. In December, 1937, she was a very severe diabetic, requiring a total of 80 units of regular insulin daily and, incidentally, the only diabetic under my observation unable to use protamine zinc insulin because of local inflammatory reactions. She had received several courses of antisyphilitic treatment in 1936 and 1937 and showed some improvement in her diabetes. In September, 1940, she was admitted to hospital showing a mild gangrene of one leg. She was controlled on 10 units of protamine zinc insulin daily. In February, 1941, there was a recurrence of her gangrene, with an increase in the severity of her diabetes, as shown in chart 4. In June, 1941, she died suddenly presumably of cardiac disease in a private home. An autopsy was not obtained.

In this case I felt that all other reasons for improvement than antisyphilitic therapy could be eliminated. This improvement was of such a degree that she was regarded as non-diabetic for some five years. That the recurrence was the result of her syphilis is open to some question, as it is quite possible that a further etiological factor, e.g., her obesity, was now playing a rôle. It is significant that her marked obesity had persisted with little change through the 13 years of my observation.

The technic of the glucose tolerance tests used in these charts consisted in the administration of 1.75 grams of glucose per kilo of actual body weight. The use of glucose tolerance curves in these cases to demonstrate changes in the degree of diabetes present is undoubtedly subject to criticism based on the known variations that may occur in these curves from other causes. Despite this, they still constitute a valuable method of comparison, and, when accompanied by other clinical and laboratory evidence, are undoubtedly significant.

One phase of this problem is perhaps even more controversial, and that is the relationship between syphilis and gangrene in the diabetic. It has been felt by many workers that there might be some connection, and Joslin [6] has apparently changed his opinion on the subject several times during the years, although his latest review denies any relationship. It has been surmised that the diabetic with tertiary syphilis may be more prone to have arterial disease and hence more likely to develop gangrene. This is a logical possibility and would appear to be borne out in this series where by using extensive methods of inquiry and investigation, syphilis was regarded as a factor in 16 of 74 cases of gangrene. This is an unusually high percentage and was only obtained by including some doubtful cases, and yet it was in some of these cases that the most significant results were obtained from antisyphilitic therapy.

Case 63. G. M., male, white, aged 60, was admitted to Highland Park Hospital, January, 1931, with gangrene of the left foot. He had been a mild diabetic for five years. Wassermann reaction was negative. Despite good control of his diabetes on diet and 40 units of insulin daily, the gangrene was progressive and amputation was performed above the knee. The stump did not heal and gangrene appeared in the right foot. Persistent questioning finally elicited a history of a penile sore and "blood treatments" in 1910. Following provocative therapy, a sub-positive Kahn reaction was obtained. On continued antisyphilitic treatment the stump commenced to heal and gangrene in the right foot disappeared. He was discharged on 35 units of insulin

daily and antisyphilitic therapy continued. His diabetic status gradually improved until in February, 1932, he was showing persistently normal blood sugar levels on a liberal diet without insulin. He was next seen by another physician in 1934 in a severe delirium tremens with a story of alcoholism over a period of several months. He had not been on a diet for several years. There was no glycosuria and fasting blood sugar was 112 mg. His further course is unknown.

Treatment

These cases were treated for their diabetes in a routine manner according to the methods of 1928–1933, with the exception of certain selected cases in which neither diet nor insulin was used. Here an effort was made to eliminate possible improvement from other causes than antisyphilitic therapy.

The treatment followed was the usual routine for tertiary syphilis. Bismuth salicylate was the drug of choice, used in one or two weekly injections over long periods. Iodides were used freely, at times being the only drug used. No benefit was noted from the use of iodides alone. Mercury was not used in most cases. Arsenicals were used when and where indicated, the majority of the treated cases receiving one or two courses. No ill effects were noted from arsenicals. It is my impression that the belief that the use of arsenicals is contraindicated in diabetes dates back to the pre-insulin days, when the poorly controlled diabetic with a low glycogen reserve was very likely to develop liver damage. Generally speaking, our present day diabetic, even of a severe grade, tolerates arsenicals well.

Pathology

Two cases only in this series have come to postmortem examination.

Case 152. F. B., male, white, aged 44, was treated for syphilis at age of 18. He was a severe diabetic. Wassermann reaction on admission to the hospital was negative. He died of a ruptured gastric ulcer. The pancreas showed no significant changes, the liver a toxic hepatitis, probably the result of his peritonitis. There was no evidence of his previous syphilitic infection.

Case 62. J. P., male, white, aged 46, was a mild diabetic with a positive Wassermann reaction. He died of pyonephrosis. Autopsy showed no abnormalities in the pancreas. There was described a peculiar diffuse round cell infiltration in the liver with capillary congestion. There were lesions suggestive of syphilis in the heart and kidneys.

No conclusions can be based on such inadequate data, but the findings are of some interest. The possible rôle of syphilis in diabetes is purely speculative. The findings of Warthin and Wilson [7] in 1916 of syphilitic pancreatitis have never been duplicated. Warren in his series had no cases in which he felt that syphilis could be responsible for the changes found in the pancreas. It is probably correct to state that syphilitic pancreatitis which has been searched for as the probable pathologic lesion in cases of the association of syphilis and diabetes is rarely, if ever, present. In recent

years, however, it has been realized that the etiology of diabetes is more complex than simple pancreatic disease, dysfunction or deficiency, and tertiary syphilis may play a significant rôle in other ways.

Warren includes in his classification of anatomical causes of insulin deficiency inadequate blood supply or arteriosclerosis, although few such cases were seen in his series. This might represent the mechanism by which the pathologic lesions of tertiary syphilis could influence the severity of a diabetes. This theory is lent some weight by the increased proportion of syphilitic diabetics who develop gangrene.

The liver must be considered as a possible site of damage in certain of these cases, and central nervous system involvement may be responsible in others. More intensive postmortem studies in such a group of cases would be of great value.

Discussion

The collection of a more adequate group of cases of syphilis in association with diabetes, and a prolonged period of observation of such cases make certain phases of the subject more distinct. The time factor in the study of such a problem in diabetes is of great importance, as conclusions drawn at the end of a four year period of study of these cases were later shown to be erroneous.

Diabetes is not affected by the primary or secondary manifestations of syphilis to any greater degree than by other systemic infections. Whatever rôle syphilis may play is distinctly associated with the tertiary or latent stages of the disease; thus, the argument that diabetes should occur in congenitally syphilitic children is not valid. In this series where treatment was concentrated on a group of diabetics with some evidence suggesting latent or tertiary syphilis, unusual improvement in carbohydrate tolerance was observed in some cases where all other reasons for such improvement than the antisyphilitic treatment could be eliminated. These were frequently cases which ordinarily would not receive antisyphilitic treatment because of the lack of other evidence of syphilis. In the effort to find these latent cases it is possible that some non-syphilitics were treated.

Of utmost importance was the finding brought only by years of observation that the majority of the cases showing improvement, at some later date again showed an increase in the severity of their diabetes. Despite the one case which shows no evidence after almost 10 years of observation, I believe that the dictum "once a diabetic always a diabetic," still holds, with the exception that I would add "once a diabetic, always a potential diabetic."

Much more consistent and dramatic results have been described by Newburgh and Conn [8] in a group of obese diabetics, where studies of 21 cases before and after weight reduction showed definitely diabetic types of curves reverting to normal in all cases. In a later paper,[9] Newburgh reports that 77 per cent of adult obese hyperglycemic patients, 47 in all, showed normal glucose tolerance tests after adequate weight reduction. It must be em-

phasized that Newburgh does not regard this group as instancing true diabetes. Dr. Frank Allen, in discussing this work, suggested the advisability of reporting the fate of these cases after five, or even 20 years. The 20 year period would not be too long if my experience with the present series is taken as a criterion. The authors, however, made the valuable observation that attributing diabetes to a pancreatic abnormality is far too restricted a conception, and that clinical investigators must now attempt to discover the specific cause of the hyperglycemia in all patients who present the classic signs and symptoms of the disease to which the term "diabetes" is attached.

Observation of the syphilitic group has led to consideration of the theory that diabetes rarely, if ever, develops in an individual who is not born with a potential defect in carbohydrate metabolism. At one time I would have attributed the potential defect to a low reserve insulin production, but the problem has become much more complex with our knowledge of the rôle of the pituitary gland and liver. Many of such potential diabetics may never develop diabetes, whereas others as a result of the presence of any of the classical so-called causes of diabetes, as obesity, hyperthyroidism, gall-bladder disease, etc., would develop clinical signs of diabetes. With the treatment and removal of these precipitating factors, they might again become clinically non-diabetic until such time as further damage occurred or unusual strain was thrown on their insulogenic mechanism. This has been demonstrated in obesity, in gall-bladder disease, in hyperthyroidism, and, I believe, this series suggests that similar results may occur in tertiary syphilis.

Summary

By exhaustive investigation for the presence of latent as well as active syphilis, 54 possible cases of syphilis were found in a group of 550 diabetics seen at Receiving Hospital, Detroit. Factors of color and sex were relatively unimportant, but the presumably syphilitic group was unduly concentrated in the later decades of life. The diabetes in the syphilitic group tended to be unusually mild.

Nineteen cases of latent or tertiary syphilis were given prolonged antisyphilitic treatment under careful observation and, where possible, this was followed by glucose tolerance tests. In some cases, when feasible, no diabetic treatment, as diet or insulin, was prescribed. These cases were then observed for varying periods up to 12 years for changes in their diabetic status. Fourteen cases showed varying degrees of improvement in tolerance, from moderate to a degree where apparently no diabetes was present. In one case no evidence of diabetes was present after 10 years.

The series suggests that there is some relationship between latent syphilis in the diabetic and the occurrence of gangrene. Syphilis should be suspected in the mild diabetic who develops gangrene, even in the presence of a negative serologic reaction. Careful histories and studies of the effect of antisyphilitic therapy may be necessary.

Even where the most marked improvement was found, there was a tendency in later years for the diabetes to reappear. It is suggested that tertiary syphilis, as well as all other so-called causes of diabetes, is merely a precipitating factor in the potential diabetic.

Note: The word "diabetes" is used to apply only to diabetes mellitus.

BIBLIOGRAPHY

1. Paullin, J. E., and Bowcock, H. M.: Treatment of syphilis co-existent with condition simulating diabetes, Jr. Am. Med. Assoc., 1924, lxxxii, 702–705.
2. Lemann, I. I.: Diabetes mellitus, syphilis and the negro, Am. Jr. Med. Sci., 1921, clxii, 226.
3. Lemann, I. I.: Relation of syphilis and diabetes to one another, Am. Jr. Syph., 1929, xiii, 70.
4. Williams, J. R.: Diabetes and syphilis . . . a critical study of relation to each other in 1000 cases of diabetes, N. Y. State Jr. Med., 1941, xli, 252–255.
5. McDaniel, L. T., Marks, H. H., and Joslin, E. P.: Diabetes mellitus and syphilis: study of two hundred and fifty-eight cases, Arch. Int. Med., 1940, lxvi, 1011–1051.
6. Joslin, E. P., Root, H. F., White, Priscilla and Marble, Alexander: Treatment of diabetes mellitus, 6th Ed., 1937, Lea and Febiger, Philadelphia.
7. Warthin, A. S., and Wilson, V. F.: Coincidence of diabetes and syphilis, Am. Jr. Med. Sci., 1916, clii, 157.
8. Newburgh, L. H., and Conn, J. W.: A new interpretation of hyperglycaemia in obese middle-aged persons, Jr. Am. Med. Assoc., 1939, cxii, 7.
9. Newburgh, L. H.: Control of the hyperglycaemia of obese "diabetics" by weight reduction, Ann. Int. Med., 1942, xvii, 935.

CIRRHOSIS OF THE LIVER; AN ANALYSIS OF 71 CASES *

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This study represents an analysis of 71 patients with portal cirrhosis observed at the U. S. Marine Hospital, Detroit from 1926 to the present, with particular reference to clinical manifestations. An excellent comprehensive review of the natural history of Laennec's cirrhosis of the liver has been published recently by Ratnoff and Patek,[1] who included a bibliography of the recent literature. In order to avoid duplication, we shall limit our comments primarily to statistical analysis of the case material, with but brief amplification upon theoretical considerations.

Material

The 71 cases analysed consist of 21 cases wherein the diagnosis of portal cirrhosis was confirmed by liver biopsy (three cases) or by autopsy (18 cases), and 50 cases with strong presumptive evidence of portal cirrhosis; cases in which the diagnosis was equivocal were excluded. Two cases of hemochromatosis and one case of cirrhosis following carbon tetrachloride poisoning were observed during the same period, but they are not included in this series because they could not be classified as portal cirrhosis.

Of the 71 patients, 29 died in the hospital and 42 were sufficiently improved to be discharged from the hospital. In view of the migratory nature of the clientele of the hospital, follow-up studies are unsatisfactory, and conclusions must, therefore, be drawn from the hospital records only in the majority of instances.

Etiologic Factors

(*1*) *Age.* The age distribution of the patients by five-year groups is presented in table 1. The average age on admission of the 71 patients

Table I

Age Distribution of 71 Patients with Cirrhosis of the Liver

Years	Number of Patients
36–40	9
41–45	14
46–50	24
51–55	16
56–60	4
61–65	2
66–70	1
71–75	1

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From the Medical Service of the U. S. Marine Hospital, Detroit, Michigan.

was 48.4 years, the youngest being 36 years old, and the oldest 73 years. It is apparent that the majority of the patients (54, or 77 per cent) was between the ages of 41 and 55 years, the peak of incidence being between 46 and 50 years, which is in fairly close agreement with the findings of others.[1, 2] Therefore, it is evident that the incidence is maximal in the fifth and sixth decades.

(*2*) *Race.* Of our 71 patients, 22 (31 per cent) were of American descent, 12 (17 per cent) of German descent, eight (11 per cent) of Irish descent, seven (10 per cent) of Polish descent, and two (3 per cent) each of Belgian and Italian descent; the other 18 patients were of mixed or unknown descent. The racial incidence of portal cirrhosis is of uncertain significance as an etiologic factor in any one reported series, since the reported incidences must be corrected in the light of the racial distribution of the hospital population.

(*3*) *Sex.* All of our 71 patients were males; however, since less than 10 per cent of our hospital population is female, we can draw no conclusions as to sex incidence. (The usually accepted ratio is two or three males to each female with cirrhosis of the liver.)

(*4*) *Occupation.* Nineteen of the patients were merchant seamen, who are usually "spree" drinkers; 24 were laborers; and five were bartenders. The remaining 23 patients were engaged in miscellaneous occupations. The rather high incidence of seamen is due to the selection of beneficiaries of the Marine Hospital Division of the U. S. Public Health Service. The high incidence among laborers and bartenders is in accordance with accepted experience.

(*5*) *Alcoholism.* The consumption of alcohol by the patients studied is summarized in table 2. It is apparent that 56 of the 71 patients (79 per cent) were habitually addicted to the use of alcoholic beverages. One of the patients, a 63 year old tavern keeper, admitted drinking about one pint of whiskey, 20 to 30 glasses of beer, and 10 to 12 glasses of wine daily for about 30 years, and there was little reason to doubt his veracity.

TABLE II

Alcohol Consumption of Patients with Cirrhosis

Consumption of Alcohol	Number of Patients
1. Abstainers	7
2. Occasional drink (beer or whiskey)	8
3. Habitual indulgence	
(*a*) In moderation (e.g., 2–4 drinks daily)	8
(*b*) Moderately excessive (e.g., 5–7 drinks daily)	17
(*c*) Excessive indulgence	31

The significance of alcoholic indulgence as a factor in producing cirrhosis of the liver has long been a moot question and it would serve no purpose to repeat here the arguments pro and con, since the subject has recently been reviewed thoroughly by Jolliffe and Jellinek.[3] They concluded that the association between chronic alcoholism and cirrhosis is definitely established, but

that alcohol is not a *direct* cause of cirrhosis, and none of the theories of *indirect* causation heretofore advanced (i.e., exogenous toxins other than alcohol present in alcoholic beverages, gastric disturbances, general metabolic disturbances of toxic nature, vitamin deficiencies, or transition from fatty liver to cirrhosis) is, of itself, sufficient to explain the association. The investigations of Connor [4, 5] indicate that excessive indulgence in alcohol may lead to fatty infiltration of the liver by virtue of the toxic action of alcohol on tissue oxidative processes, plus the relative starvation and the vitamin deficiencies which are so frequently found in association with chronic alcoholism. The fatty infiltration may cause atrophy and degeneration of the liver cells, with subsequent replacement by fibrous tissue and the development of hepatic cirrhosis.

In our series, fatty infiltration in association with portal cirrhosis was present in eight out of 21 livers examined microscopically. However, the absence of fat cannot be used as an argument against the significance of fatty infiltration of the liver as a step in the pathogenesis of cirrhosis, because terminal exhaustion of body fat, or the cessation of indulgence in alcohol, or the use of a high-protein, high-carbohydrate diet or other lipotropic factors may promote resorption of liver fat.[4, 6]

(*6*) *Syphilis.* Nineteen (27 per cent) of the patients in this group had positive blood Kahn reactions, or a history of a primary lesion, or both. Only six of these patients had received arsenical antisyphilitic therapy previously. Schumacher [7] reviewed the significance of syphilis as a causative factor in cirrhosis of the liver and concluded that syphilis with, and possibly without, associated alcoholism may cause a diffuse cirrhosis of the liver.

Of the 19 patients in this series with evidence of syphilis, 18 were habitual imbibers of alcoholic beverages. The actual coexistence of alcoholism and syphilis in this series is 25.4 per cent, whereas the chance expectancy of such coexistence is 21.1 per cent. None of the livers examined presented a picture typical of syphilitic cirrhosis.

What significance the use of arsenicals in the treatment of syphilis may have in the development of cirrhosis is not clear, since 13 of the 19 patients who had syphilis and cirrhosis had not been treated with arsenicals. The crux of the problem is aptly presented by Baldridge: "Vices are prone to be multiple, so that alcoholism, syphilis, and antisyphilitic treatment often coexist in the history of patients with cirrhosis of the liver." [8]

(*7*) *Heart Disease.* Organic heart disease was present in 10 of the 71 cases, 15 per cent (one case of rheumatic heart disease, two of hypertensive heart disease, and seven of arteriosclerotic heart disease). However, in only four of these cases was there evidence of congestive heart failure. The detection of congestive failure in association with cirrhosis of the liver is a difficult clinical problem, since dependent edema is common in cirrhosis, and dyspnea and orthopnea may result from ascites or hydrothorax in cirrhosis. Katzin and his co-workers [9] have reviewed "cardiac cirrhosis" and con-

cluded that it is clinically a relatively rare condition, although chronic passive hepatic congestion secondary to congestive heart failure frequently causes an increase in hepatic fibrous tissue. The fibrosis may be central or portal or both, and is directly proportionate to the duration of the heart failure.

Each of the four patients in our series who had congestive heart failure and cirrhosis was also a habitual alcohol imbiber, so the influence of the cardiac factor in this series is highly equivocal.

(*8*) *Previous Hepatic Disease.* Only one patient in this series had a history of an episode of previous jaundice, which occurred 28 years prior to his hospitalization with cirrhosis.

The conception of cirrhosis as an inflammatory process which may be acute or chronic and may have long periods of latency has been advanced.[10] The possibility that an infectious process may be responsible for the inflammatory changes described in some cases of cirrhosis [11] is unproved. The occurrence of fever, leukocytosis, and elevated erythrocyte sedimentation rates in many of the patients in this group tends to support the concept of the inflammatory character of the pathologic process, at least in certain cases.

(*9*) *Toxic Agents.* The six patients who received arsenical antisyphilitic treatment have already been mentioned, and each of these patients was a chronic alcohol addict; therefore, the influence of arsenic in this series is questionable, except that the arsenicals may have rendered the liver more susceptible to the toxic action of alcohol (or vice versa).

None of the 71 patients with portal cirrhosis presented here had a history of exposure to lead, cinchophen, chloroform, tetrachlorethane, copper, or other hepatotoxic agents implicated in the literature as etiologic agents in cirrhosis of the liver.

(*10*) *Metabolic and Endocrine Factors.* Diabetes mellitus of mild degree was present in one patient. Connor [4] has commented on the rôle of diabetes mellitus in causing fatty infiltration of the liver, and the possible subsequent development of cirrhosis.

Hyperthyroidism was not present in any of the cases in this series, but impairment of liver function and cirrhosis of the liver have been reported in association with thyrotoxicosis.[12]

Gynecomastia (unilateral) was present in one patient but he had no other discernible endocrinopathic stigmata. Glass and his co-workers [13] reported eight cases of gynecomastia occurring in cirrhosis of the liver, and the foreign literature contains many references to this association. No other evidences of endocrinopathy were present in our series. Loss of body hair has been considered a feature of cirrhosis of the liver, but did not occur in any significant degree in our patients.

(*11*) *Diet.* Insufficient data were available with respect to the dietary habits of these patients to attempt to evaluate the importance of the dietary factor in this group.

However, recent experimental investigation has indicated the importance of adequate dietary protein in increasing resistance to hepatotoxic agents,

and the usually inadequate diet of the chronic alcohol addict is indubitably a significant factor predisposing to the development of cirrhosis.

(*12*) *Other Factors.* The rôle of malaria, enteric fevers, and tuberculosis in cirrhosis of the liver has been reviewed by Ratnoff and Patek.[1] With the exception that seven patients (10 per cent) of the series had had typhoid fever, these factors were not present to a significant degree in our patients.

No other significant etiologic factors were revealed by analysis of the series of cases presented here.

Clinical Features

The incidences of the various symptoms referable to cirrhosis are presented in table 3, where they are considered in the light of general incidence,

Table III

Incidence of Complaints in Patients with Portal Cirrhosis

Complaint	Number of Patients		
	A	B	C
Ascites	39	31	22
Abdominal pain	34	8	12
Edema	34	9	13
Nausea and vomiting	31	1	5
Weakness	27	9	9
Jaundice	27	8	10
Weight loss	24	1	3
Gastrointestinal hemorrhage	15	4	3
Dyspnea	15	0	1
Constipation	8	0	0
Diarrhea	8	0	0
Epistaxis and/or ecchymosis	7	0	0
Rectal discomfort (hemorrhoids)	2	1	1
Hematuria	1	0	0

Column A—General incidence
Column B—Incidence as presenting (or chief) complaint
Column C—Incidence as earliest complaints referable to cirrhosis

incidence as presenting complaint, and incidence as earliest complaint referable to cirrhosis. The incidence of positive physical findings is presented in table 4. Analysis of the clinical features in this fashion permits some interesting observations.

Several patients had more than one presenting complaint referable to cirrhosis (e.g., abdominal enlargement and jaundice). Three patients had no such complaints on admission, cirrhosis being an incidental finding at autopsy in two; the third patient entered the hospital for an elective hernioplasty, but examination revealed fever (of spiking character), marked hepatomegaly, severe anemia (2.5 million red blood cells per cu. mm.), and leukocytosis (25,000 white blood cells per cu. mm.), and a liver biopsy specimen showed well-advanced cirrhosis.

Ascites. Abdominal enlargement due to accumulation of ascitic fluid was the earliest complaint of 22 patients (31 per cent). It was the chief complaint at the time of admission in 31 cases, and an incidental complaint

TABLE IV

Incidence of Physical Signs in Patients with Portal Cirrhosis

Sign	Number of Patients
Hepatomegaly	49
Ascites	44
Edema	42
Jaundice	37
Fever	35
Dilated superficial veins	29
Anemia	25
Malnutrition	24
Hemorrhoids	24
Splenomegaly	17
Nervous disturbances	15
Hydrothorax	7
Umbilical hernia	7
Inguinal hernia	5

in eight others, making a total of 39 patients (55 per cent) who *complained* of ascites. In addition, five patients were found to have free intraabdominal fluid on physical examination, bringing the total number of patients with ascites to 44 (63 per cent). Cirrhosis with ascites has been termed "decompensated" cirrhosis.

The ascites of hepatic cirrhosis is probably due to the combined action of increased portal pressure [14] and decreased serum colloid osmotic pressure [15] secondary to the hypoalbuminemia commonly found in cirrhosis of the liver. Hypoproteinemia, primarily due to a lowered serum albumin content, with decrease or inversion of the A/G ratio, was a common finding in these patients, and frequently has been reported in cirrhosis of the liver.[16, 17, 18, 19]

Ascites was present in association with jaundice in 28 patients. Both jaundice and ascites have been considered ominous prognostic signs. In 18 patients who died in the hospital the duration of life from the onset of ascites was known, and averaged 7.5 months, with a range of 23 days to 38½ months. That ascites is not necessarily a fatal omen is indicated by the wide range, plus the fact that we have had under observation a patient whose initial complaint was ascites which developed in February 1938 and has recurred and subsided intermittently since that date; this patient is at present in a latent phase clinically. The observations of Fleming and Snell [2] on the treatment of portal cirrhosis with ascites also indicate that a more hopeful outlook is possible than has been entertained heretofore.

Abdominal Pain. Thirty-four patients (48 per cent) complained of abdominal pain during the course of their illness; in 12 patients, it was the earliest difficulty noted; and in eight patients it was the presenting complaint. The pain was usually a dull persistent aching sensation in the abdomen, particularly in the epigastrium, aggravated by the ingestion of food, and not relieved by the usual antacid medications and carminatives. In most cases, the pain could be attributed to the displacement and compression of the hollow viscera by hepatomegaly and ascites, or to functional gastrointestinal disturbances resulting from the impairment of the portal circulation. Fre-

quently, flatulence and "gas cramps" presented premonitory signs of the development of ascites. In nine patients abdominal pain was present without ascites; in three of these patients there was roentgenographic evidence of a duodenal ulcer; and a fourth patient had evidence of impaired cholecystic function as gauged by the dye excretion test. The remaining five patients without ascites were chronic alcohol addicts, and the pain may have been due, partially at least, to digestive disturbances secondary to the alcoholism. One patient with ascites and abdominal pain was found at autopsy to have chronic cholecystitis with cholelithiasis and a gastric ulcer. The frequency of coincidence of peptic ulcer or gall-bladder disease with cirrhosis of the liver has been discussed by Ratnoff and Patek.[1]

Edema. Edema of the lower extremities was noted by 34 patients, but was evident on physical examination in 42 (59 per cent). It was the earliest symptom in 13 patients, and the presenting complaint of nine patients. The edema involved the scrotum and lower abdominal wall in four patients, but there were no instances of edema of the face or upper extremities.

The most widely accepted explanation of the occurrence of edema in hepatic cirrhosis is that it is due either to (1) increased venous pressure in the lower extremities as a result of increased intraabdominal pressure (ascites), or (2) coexistent congestive failure. However, edema was present in the absence of ascites in nine patients in this series, in only two of whom were there evidences of congestive heart failure. The edema is, therefore, probably due primarily to hypoproteinemia,[16] with increased venous pressure as a significant factor only in those cases with massive ascites.

Enlargement of the Liver and Spleen. A palpable liver was found in 49 patients (70 per cent) and was the most common physical finding in this series. The average weight of the liver in the patients examined post-mortem was 2207 gm., the weight varying from 915 gm. to 4420 gm. As has already been noted, fatty infiltration was evident microscopically in eight of 21 livers examined. Although fatty infiltration may be responsible for hepatomegaly in many cases, it was not always found in the enlarged livers, and, vice versa, excessive fat was occasionally demonstrable in relatively small livers. Analyses of the fat and protein content of several livers from this series have been reported in connection with another study.[20]

The spleen was palpable in 17 patients (24 per cent) in this series, primarily as a result of congestion secondary to impaired portal circulation. Fibrosis of the spleen was evident on microscopic examination in five cases. The weight of the spleen in the patients examined post mortem averaged 395 gm. and varied from 150 gm. to 800 gm.

Jaundice. Jaundice was noted by 27 patients (38 per cent), being the earliest manifestation of cirrhosis in 10 patients, and the presenting complaint of eight. Physical examination revealed icterus in an additional 10 patients, bringing the total of jaundiced patients to 37 (52 per cent). Of 44 patients in whom the icteric index was determined, 28 had values of 10 units or higher, and 15 had values of 30 units or higher. Pruritus was a fre-

quent accompaniment of the higher degrees of jaundice, but clay-colored stools were rarely noted. Jaundice was present without ascites in 11 patients.

The presence of jaundice has been interpreted as an indication of activity of the disease process.[1] That jaundice is a sign of an advanced stage of the disease is indicated by the fact that the average duration of life after the onset of jaundice in the patients of this series who died in the hospital was 8.7 months, and that 63 per cent of the patients who died in the hospital were jaundiced. However, the jaundice may be intermittent, or may clear entirely. Jaundice was present in 17 (40 per cent) of the 42 patients who improved sufficiently to warrant discharge from the hospital, and the jaundice subsided before they were discharged.

Weight Loss. Loss of weight was one of the complaints of 24 patients (34 per cent), constituting the presenting complaint of one patient, and the earliest manifestation noted in three. Malnutrition was evident on physical examination in 24 patients, but these were not in all instances patients who complained of weight loss. The frequency of weight loss is difficult to evaluate since the accumulation of ascitic fluid or the development of edema may mask the wasting of flesh which occurs.

Emaciation, protuberant abdomen, sunken cheeks and temporal hollows, scleral icterus, a sallow complexion and facial telangiectasia constitute a characteristic clinical picture, and the diagnosis of hepatic cirrhosis may frequently be suspected from observation alone.

Fever. Temperature elevation for which the cause was not apparent was present in 35 cases (49 per cent). The fever was usually low-grade and of intermittent character and possibly reflected active inflammatory and degenerative processes in the liver parenchyma.

Gastrointestinal Disturbances. Abdominal pain, nausea, vomiting, and disturbances of bowel motility were the commonest evidences of disturbed gastrointestinal function. Abdominal pain has already been discussed. Nausea and vomiting occurred in 31 patients (44 per cent), constituting the earliest complaints of five patients, but the presenting complaints of only one. Eight patients complained of persistent constipation, and an equal number were distressed by diarrhea.

The occurrence of these difficulties is readily understandable when the abdominal contents are compressed by ascitic fluid. However, in 15 patients with gastrointestinal disturbances, ascites was absent and the dysfunctions were probably due to the impairment of the portal circulation.

Gastrointestinal Hemorrhage. Hematemesis occurred in 15 patients (21 per cent) and was the presenting complaint of four patients, in three of whom it was also the earliest manifestation of cirrhosis. Melena was noted terminally in two other patients. Despite the difficulty of demonstrating bleeding points at autopsy examination, it is believed that the hematemesis occurring in cirrhosis is due almost always to rupture of esophageal varices, although in one patient in this series gastric varices were evident at postmortem examination.

Hematemesis, although an alarming occurrence, is not necessarily a fatal one, since seven of the 15 patients with hematemesis were among the group that improved and were discharged from the hospital. In eight patients the occurrence of gastrointestinal hemorrhage was followed by the gradual development of coma ending in death. Elevation of the blood non-protein nitrogen was observed after hemorrhage into the intestinal tract in three instances.

Dyspnea. Fifteen patients (21 per cent) complained of dyspnea; in four cases the dyspnea was attributable to congestive heart failure. In six other cases limitation of diaphragmatic excursion by ascites was considered responsible for the shortness of breath. In two patients accumulation of pleural fluid explained the dyspnea. In three instances, no ascites, hydrothorax, or congestive failure was found, and the etiology of the dyspnea here is not clear. Snell [21] observed reduction in the oxygen saturation of arterial blood in patients with chronic hepatic disease, and Darling [22] found that in six of 34 patients with cirrhosis slight degrees of arterial oxygen unsaturation were present which could not be explained by pulmonary disease. Possibly the unexplained dyspnea in the three instances noted above may be related to changes in properties of hemoglobin.

Weakness. Ready fatigability and weakness were specific complaints in 27 cases (38 per cent). It was the earliest difficulty noted by nine patients, and the presenting complaint of nine patients. However, some degree of weakness was probably present in a much greater number of cases than is evident from these figures. As might be anticipated, weakness and weight loss were commonly associated, but in most instances the weakness antedated the loss of weight.

Hemorrhoids. Rectal discomfort, dyschesia, or bleeding due to hemorrhoids were noted by only two patients. In one case, hemorrhoids were the presenting complaint; in the other, the hemorrhoids were the earliest difficulty noted. Physical examination, however, revealed dilated and protruding hemorrhoidal veins in 24 patients (34 per cent).

The occurrence of hemorrhoids in hepatic cirrhosis probably reflects the development of collateral circulation to aid the impaired portal drainage, although hemorrhoids are a relatively frequent finding in these age groups. That increased intra-abdominal pressure due to ascites may cause stasis in the hemorrhoidal veins is suggested by the fact that 18 of the 24 patients with hemorrhoids had ascites.

Umbilical and Inguinal Hernias. An umbilical hernia was found in seven patients (10 per cent). Each of these patients had massive ascites, and the hernia was undoubtedly due to the mechanical effects of the increased intra-abdominal pressure.

Inguinal hernias were observed in five patients (7 per cent), four of whom had ascites, and probably the same mechanism is partially responsible, although inguinal hernias are fairly common in patients of these age groups.

Dilated Superficial Veins. Prominence of the veins of the anterior ab-

dominal wall was evident in 29 patients (41 per cent) and reflected the development of collateral channels between the portal and systemic circulations.

Hematuria. Hematuria occurred in one case in this series and was attributed to rupture of a urethral varix. Libman, in discussing Christian's paper,[23] mentions rupture of distended vesical veins as a cause of hematuria occurring in cirrhosis of the liver.

Bleeding Tendencies. Epistaxis, purpura, ecchymosis, or bleeding from the gums occurred in seven patients (10 per cent), generally in association with clinically severe stages of the disease. In this series, hemorrhagic tendencies (exclusive of gastrointestinal hemorrhages) were observed only in jaundiced patients. The hemorrhagic phenomena exhibited by patients with cirrhosis of the liver are considered due to the hypoprothrombinemia which results from the inability of the damaged liver to manufacture prothrombin, even in the presence of vitamin K.

It has been suggested that mucosal angiomata may explain certain instances of bleeding.[1] The vascular "spider" associated with cirrhosis of the liver has been adequately described by Patek and co-workers.[24]

Hydrothorax. Accumulation of fluid in the pleural cavities occurred in seven patients (10 per cent). In six patients the effusion was evident on clinical or roentgenologic examination, while in the seventh it was found at autopsy examination. The effusion was bilateral in two patients, and unilateral in five (involving the left pleural cavity in two, and the right in three). All patients with pleural effusion also had ascites, and none of these presented evidence of cardiac disease. In two patients, the hydrothorax dominated the clinical picture and required frequent thoracenteses. In one instance, the pleural fluid was grossly bloody.

The mechanism underlying the development of hydrothorax in cirrhosis of the liver is not clear. Mallory [25] believes that in many cases there is a fairly free passage of fluid through the diaphragm, and in one of our patients thoracentesis usually resulted in an obvious decrease in the degree of ascites; the autopsy examination in this case disclosed no gross evidence of abnormality of the diaphragm. Increased capillary permeability has been advocated as an explanation for the hydrothorax occurring in cirrhosis, but Smirk [26] failed to find increased capillary permeability in cirrhosis. Decreased colloidal osmotic pressure, and mechanical interference with pulmonary circulation due to ascites have also been suggested as causes of hydrothorax in the absence of tuberculosis or renal or cardiac dysfunction.

Bloody pleural effusion occurring in cirrhosis of the liver has been reported previously by Christian,[23] who mentions other similar cases. The blood in the pleural fluid might be due to the bleeding tendencies of patients with cirrhosis.

Nervous Disturbances. The development of nervous disturbances progressing from restlessness to delirium and coma ending in death occurred in 15 patients (21 per cent), exclusive of the cases in which coma developed after massive hemorrhage. Coma has long been recognized as a frequent

manner of exodus of patient with cirrhosis, and transient paralyses and abnormal reflexes have been observed in such comatose patients. Because of the similarity of the neurologic findings to those of alcoholic encephalopathy, it has been suggested that the neurological changes might be due to a biochemical disorganization of the enzyme systems necessary for carbohydrate metabolism.[27]

In six of the 15 patients dying in coma, the development of stupor progressing to coma followed within a few hours the administration of morphine sulfate in dosage of 1/6 to 1/4 grain, and apparently was precipitated by the opiate (administered for pain or other indications). Mallory [28] mentioned that patients with cirrhosis may develop fatal coma after a single dose of morphine. Morphine is probably detoxified by conjugation with glucuronic acid in the liver,[29, 30] and it seems logical to assume that the cirrhotic liver may be unable to combine the glucuronic acid with the morphine, permitting the passage of free morphine, which may be more active pharmacologically than bound morphine (although this latter supposition is as yet unproved). However, it must be mentioned that in several other patients with cirrhosis, morphine had been administered intermittently frequently for the treatment of gastrointestinal hemorrhage or other indications, without apparent injurious effects. The effect of morphine in the causation of coma is not absolutely clear, but it seems wise to interdict the use of opiates in cirrhosis when less potent drugs may serve similar purposes.

Changes in Blood Count. A red blood count of less than four million cells per cu. mm., or a hemoglobin of less than 80 per cent or both, was found in 25 (53 per cent) of 47 patients for whom data were available. The color index was greater than one in 14 instances, and less than one in 11 instances.

The white blood cell count was above 10,000 cells per cu. mm. in 14 of 53 patients (26 per cent); in 10 of these 14 patients no cause for the leukocytosis was apparent, other than the cirrhosis of the liver. The differential counts were not unusual.

The erythrocyte sedimentation rate was determined in 30 patients and was increased beyond 20 mm. in an hour in 19 instances (63 per cent). The elevation of the sedimentation rate probably reflects inflammatory changes in hepatic parenchyma, and possibly alterations in plasma proteins.

Elevation of the Blood Non-Protein Nitrogen. Discussion of changes in blood chemistry and tests of liver function is beyond the scope of this paper, but it is of interest to note that the blood non-protein nitrogen was determined in 36 patients, and was elevated to 45 mg. per 100 c.c. or higher in seven instances (10 per cent). Jaundice was present in every patient with azotemia; in three instances, the elevation of the non-protein nitrogen was associated with hemorrhage into the gastrointestinal tract. Five of the seven patients with azotemia in this series died. Meyer and co-workers [31] have called attention to the significance of elevation of the non-protein nitrogen in jaundiced patients as a prognostic indication.

Cause of Death. In the 29 patients who died in the hospital, the average

duration of life from the development of the initial complaint referable to cirrhosis to the time of death was 11 months, and varied from two weeks to three years. In 15 patients, death was due to progressive "hepatic insufficiency," a vague nondescript term implying progressive failure of liver function and the gradual development of coma ending in death. Eight patients died from massive gastrointestinal hemorrhage. Four patients died of intercurrent infection (two of pneumonia, one of peritonitis, and one of streptococcal meningitis). In two cases the cause of death was uncertain.

Summary

1. The case histories of 71 patients with portal cirrhosis were reviewed with particular reference to etiologic factors and clinical findings.

2. The etiologic significance of age, alcoholism, and syphilis is found to be in accordance with previously accepted conceptions.

3. Fever, leukocytosis, and elevated sedimentation rate were found in a significant number of patients, and probably represent active inflammatory changes in the liver.

4. The possible relationship of the administration of morphine to the development of hepatic coma is discussed briefly.

BIBLIOGRAPHY

1. Ratnoff, O. D., and Patek, A. J., Jr.: The natural history of Laennec's cirrhosis of the liver—an analysis of 386 cases, Medicine, 1942, xxi, 207–268.
2. Fleming, R. G., and Snell, A. M.: Portal cirrhosis with ascites—an analysis of 200 cases with special reference to prognosis and treatment, Am. Jr. Digest. Dis., 1942, ix, 115–120.
3. Jolliffe, N., and Jellinek, E. M.: Vitamin deficiencies and liver cirrhosis in alcoholism. Part VII—Cirrhosis of the liver, Quart. Jr. Studies on Alcohol, 1941, ii, 544–583.
4. Connor, C. L.: Fatty infiltration of the liver and the development of cirrhosis in diabetes and chronic alcoholism, Am. Jr. Path., 1938, xiv, 347–364.
5. Connor, C. L.: The etiology and pathogenesis of alcoholic cirrhosis of the liver, Jr. Am. Med. Assoc., 1939, cxii, 387–390.
6. Frame, E. G.: Lipotropic substances, Yale Jr. Biol. and Med., 1942, xiv, 229–255.
7. Schumacher, G. A.: Causative factors in the production of Laennec's cirrhosis with special reference to syphilis, Am. Jr. Med. Sci., 1937, cxciv, 693–700.
8. Baldridge, C. W.: The relationship between antisyphilitic treatment and toxic cirrhosis, Am. Jr. Med. Sci., 1934, clxxxviii, 685–690.
9. Katzin, H. M., Walter, J. V., and Blumgart, H. L.: "Cardiac cirrhosis" of the liver —a clinical and pathologic study, Arch. Int. Med., 1939, lxiv, 457–470.
10. Bloomfield, A. L.: The natural history of chronic hepatitis (cirrhosis of the liver), Am. Jr. Med. Sci., 1938, cxcv, 429–444.
11. Moon, V. H.: Histogenesis of atrophic cirrhosis, Arch. Path., 1932, xiii, 691–706.
12. Shaffer, J. M.: Diseases of the liver in hyperthyroidism, Arch. Path., 1940, xxix, 20–30.
13. Glass, S. J., Edmondson, H. A., and Soll, S. N.: Sex hormone changes associated with liver disease, Endocrinology, 1940, xxvii, 749–752.
14. McIndoe, A. H.: Vascular lesions of portal cirrhosis, Arch. Path., 1928, v, 23–42.
15. Butt, H. R., Snell, A. M., and Keys, A.: Plasma protein in hepatic disease, Arch. Int. Med., 1939, lxiii, 143–155.

16. MYERS, W. K., and KEEFER, C. S.: Relation of plasma proteins to ascites and edema in cirrhosis of the liver, Arch. Int. Med., 1935, lv, 349–359.
17. POST, J., and PATEK, A. J.: Serum proteins in cirrhosis of the liver, Arch. Int. Med., 1942, lxix, 67–82.
18. ISRAEL, H. L., and REINHOLD, J. G.: Detection of cirrhosis and other diseases of the liver by laboratory tests, Jr. Lab. and Clin. Med., 1938, xxiii, 588–596.
19. FOLEY, E. F., KEETAN, R. W., KENDRICK, A. B., and DARLING, D.: Alterations in serum protein as an index of hepatic failure, Arch. Int. Med., 1937, lx, 64–76.
20. FAGIN, I. D., SAHYUN, M., and PAGEL, R. W.: Cirrhosis of the liver—the lipotropic action of parenterally administered amino acids, Jr. Lab. and Clin. Med., 1943, xxviii, 987–993.
21. SNELL, A. M.: The effects of chronic disease of the liver on the composition and physico-chemical properties of blood: changes in the serum proteins; reduction in oxygen saturation of the arterial blood, ANN. INT. MED., 1935, ix, 690–711.
22. DARLING, R. C.: Arterial oxygen saturation in cirrhosis of the liver, ANN. INT. MED., 1940, xiv, 898–902.
23. CHRISTIAN, H. A.: Bloody pleural fluid, an unusual complication of cirrhosis of the liver, Trans. Assoc. Am. Phys., 1937, lii, 167–170.
24. PATEK, A. J., JR., POST, J., and VICTOR, J. C.: Vascular "spider" associated with cirrhosis of the liver, Am. Jr. Med. Sci., 1940, cc, 341–347.
25. MALLORY, T. B.: Discussion—case records of the Massachusetts General Hosp., Case No. 26441, New England Jr. Med., 1940, ccxxiii, 731–734.
26. SMIRK, F. H.: Capillary permeability in cirrhosis with hypoproteinemia, Clin. Sci., 1935, ii, 57–66.
27. SNELL, A. M.: Changing conceptions of portal cirrhosis, Pennsylvania Med. Jr., 1942, xlv, 337–344.
28. MALLORY, T. B.: Discussion, case records of the Massachusetts General Hospital, Case No. 26152, New England Jr. Med., 1940, ccxxii, 643–646.
29. OBERST, F. W.: Relationship of the chemical structure of morphine derivatives to their urinary excretion in free and bound forms, Jr. Pharmacol. and Exper. Therap., 1941, lxxiii, 401–404.
30. OBERST, F. W.: Studies on the fate of morphine, Jr. Pharmacol. and Exper. Therap., 1942, lxxiv, 37–41.
31. MEYER, K. A., POPPER, H., and STEIGMANN, F.: Significance of rise of non-protein nitrogen in medical and surgical jaundice, Jr. Am. Med. Assoc., 1941, cxvii, 847–850.

SOME NOTES ON THE TRANSMISSION OF HEART MURMURS*

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Despite the great antiquity of the practice of auscultation of the heart, it is surprising how little is known concerning the exact mechanism, production, and propagation of heart murmurs. Most of the information upon which prevailing medical teaching rests is derived from bedside observation correlated with postmortem findings. Little careful experimentation, either in man or animals, has been undertaken. Many simple questions concerning murmurs remain unanswered. Even trained experts in cardiology find great difficulty in explaining the mechanism of systolic murmurs, or in appraising their significance. This has been brought to our attention in a striking fashion during the present war when decisions have to be made concerning fitness for military duty of thousands of young men in whom the only abnormality is a systolic murmur. As examples of limitation of our knowledge one might mention several simple propositions. It would appear that with a small orifice such as is present in interventricular septal defect, or with a slight degree of mitral regurgitation, the resultant murmur (other things being the same) should be louder than if the lesion were larger. No definite proof of this observation appears to have been presented. When a systolic murmur accompanies a high degree of aortic stenosis, is the origin of the murmur in the blood itself, then transmitted to the neighboring structures, or does the sound originate in the wall of the aorta that is set in vibration, or possibly in the valve leaflets themselves? Similarly, when the mitral valve is involved, do the chordae tendineae, the papillary muscles, or the cardiac musculature itself play any rôle in the production of murmurs? It is obvious that the point of maximum audibility would be quite different if the murmur were made by the movement of the aortic valve cusps than if it were produced in the wall of the aorta. The reason that the systolic murmur in coarctation of the aorta is audible not only over the anterior chest, but in the interscapular region is that its point of production is deep in the middle of the chest, and it is transmitted in both directions. Does the gradual accentuation of a murmur, as a patient progresses from a moribund state to one of compensation, result from an increased vigor of muscular contraction, or to a decrease in dilatation of the heart and adjoining vessels? When a murmur has been produced, what is the mechanism of its transmission? Is it altogether propagated with the blood stream, and how important a factor is possible transmission through neighboring structures? Furthermore,

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what makes one murmur audible over a large area, and another remain localized over a small area? Does the pitch, entirely apart from the intensity, play a rôle in the propagation of the murmur?

One factor, not sufficiently appreciated, that must have a bearing upon the production of murmurs is the velocity of blood flow. It is reasonable to assume that when fluid moves from one chamber into another through a constriction, if the caliber of the tube suddenly becomes narrowed or widened, the speed with which this movement takes place must affect the intensity of the resultant vibration or murmur. It was previously commented on [1] that many clinical conditions, such as hyperthyroidism, fever, anemia, excitement, and exercise, all associated with an increase in velocity of blood flow, frequently are accompanied by a systolic murmur. May not this same mechanism be involved in many other conditions where the measurement of the velocity of blood flow as customarily determined is normal? After all, it is not the speed of movement of blood from *arm* to *tongue* that would have any bearing on the production of murmurs, but rather the velocity of blood flow from one chamber of the heart to another, or from the ventricles through the aorta or pulmonary artery. An illustration in point is the situation that is present with a high degree of aortic stenosis. Here the total minute output of blood, the heart rate, and the velocity of blood flow, as measured from arm to tongue, may be perfectly normal, and yet the blood must go through an extremely narrow aortic orifice. The only possible explanation for this anomalous situation is that the speed of flow from left ventricle into the aorta must be terrific. This is supported by finding a firm, huge left ventricle as a rule in such cases of aortic stenosis. Such a ventricle must be expelling blood with great force. The appearance of the presystolic murmur of mitral stenosis after effort, previously inaudible at rest, is another instance in which the production of a murmur is determined by speed of blood flow. It is a common experience that the presystolic murmur of mitral stenosis is more readily heard with the patient lying in the left lateral position, and the diastolic murmur of aortic insufficiency with the patient sitting upright. Is this due to a closer proximity to the chest wall of the tissues producing the murmur, or to an increase in the velocity of blood flow through the respective valves in these positions? The complete disappearance or absence of the diastolic murmur in some cases of advanced mitral stenosis may well be due to the reverse of the mechanism discussed above. When the left auricle is markedly dilated, especially if fibrillation is present, and there is considerable weakening of the heart, even if the mitral valve is greatly stenosed blood flow from auricle to ventricle must be very sluggish. Furthermore, residual blood is present in the chambers of such hearts in large quantities. On postmortem examination cardiac chambers often are found to contain a half liter of blood or more. Inasmuch as only about 50 c.c. of blood are propelled with each systole, it is evident that blood is delivered into cavities that are already quite full. What effect does this residual blood have upon the production and propagation of murmurs?

The entire subject of extracardiac murmurs is also very perplexing. When slight systolic murmurs are heard in patients with a thin chest wall, particularly when the antero-posterior diameter of the chest is small, can they be due to a purely mechanical contact or rubbing motion between the heart or great vessels and the chest? Furthermore, the movements of the lungs back and forth between heart and anterior chest wall may not only produce phasic cardio-respiratory murmurs, but can decrease and increase the intensity of endocardial murmurs. It, therefore, would seem fallacious to teach that a murmur that disappears or decreases strikingly with deep inspiration is necessarily unimportant or extra-cardiac.

In the interpretation of a murmur one is concerned with its location, its time in cardiac cycle, its character, and its intensity. Although the exact character of the murmur may at times be helpful, as illustrated by the continuous machinery-like noise of arterio-venous fistula, we believe that in appraising a systolic murmur the exact intensity is most important. We have advocated [2] grading intensity of murmurs from 1 to 6, 1 being the faintest that can be heard, and 6 being loud enough to be audible with the stethoscope just removed from the chest wall. As a matter of experience it has been found that systolic murmurs of grade 3 intensity or louder occur only when there is some form of heart disease, endocardial or myocardial, or in those diseases, like marked anemia, which occasionally are accompanied by murmurs. On the other hand, murmurs of grade 1 intensity (and occasionally even of grade 2 intensity) are frequently observed where most careful examination fails to reveal any organic disease of the heart or any other important organ. The difficulty is that a loud grade 5 murmur of aortic stenosis, for example, does not attain this intensity over night, and must have gone through the stage when it was only grade 1. It is during these early stages of the development of murmurs that our diagnostic criteria are very inadequate.

It is clear from the above that many important questions concerning cardiac murmurs remain unanswered. The purpose of this study is to present some data concerning one or two of the above points. First, we will present evidence to show that murmurs are transmitted through bone, and that very likely the transmission through blood stream is unimportant, and, secondly, that the disappearance or marked decrease in intensity of a murmur with deep inspiration does not mean that it is "functional."

For many years it has been our growing conviction that the transmission of murmurs is mainly, if not entirely, a function of intensity, i.e. loud murmurs are widely distributed and faint ones are not. The current teaching that aortic systolic murmurs are transmitted to the neck and mitral systolic murmurs to the axilla has the connotation that murmurs are transmitted with the blood stream. From a purely physical point of view it seems illogical to assume that sound is transmitted in the direction of and with the blood stream, for the speed of transmission of sound through liquid is much faster than the velocity of blood flow. Therefore, the transmission that

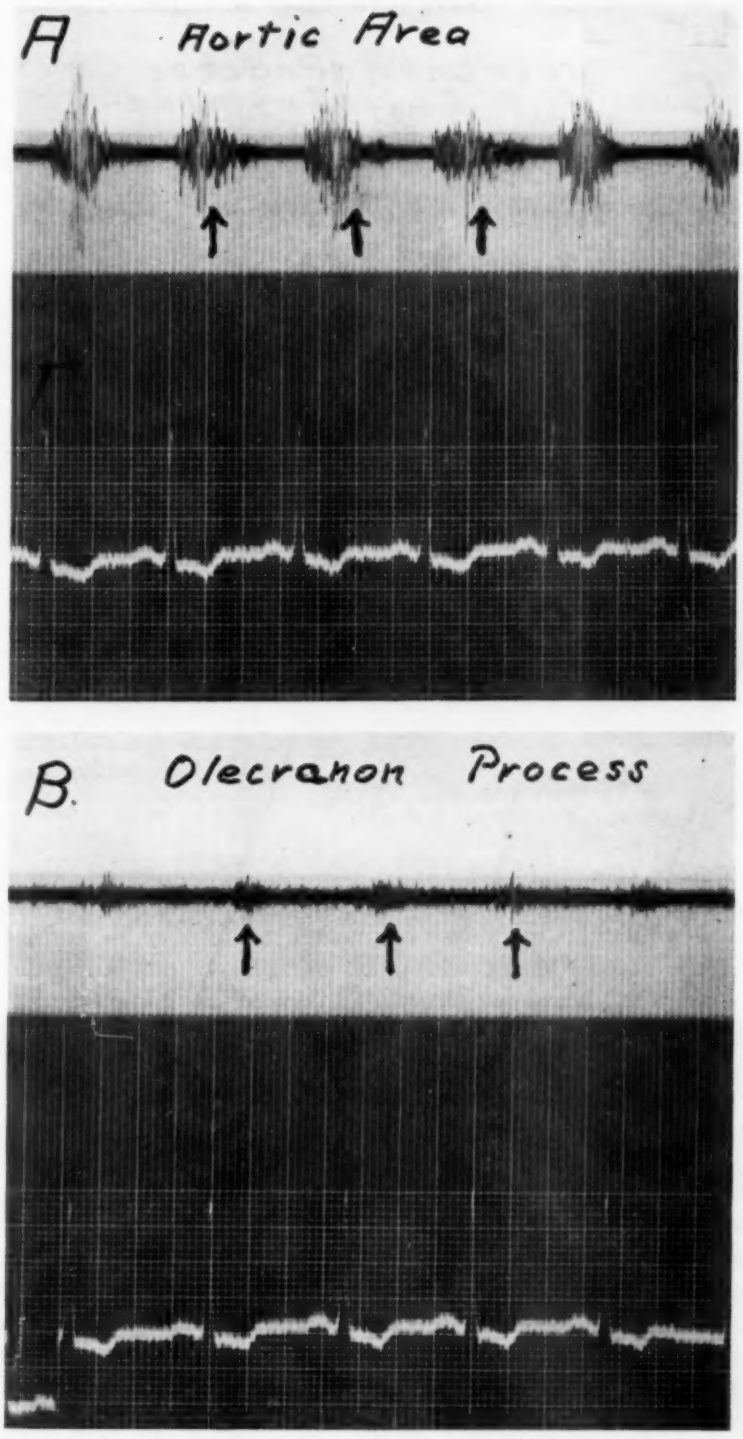


FIG. 1, A and B. Simultaneous phonocardiograms and electrocardiograms on a woman, aged 38, with marked aortic stenosis. Record A was obtained from the aortic area, and shows marked systolic murmur (arrows). Record B was from the right olecranon process and shows definite systolic murmur coming slightly later than the aortic murmur (arrows).

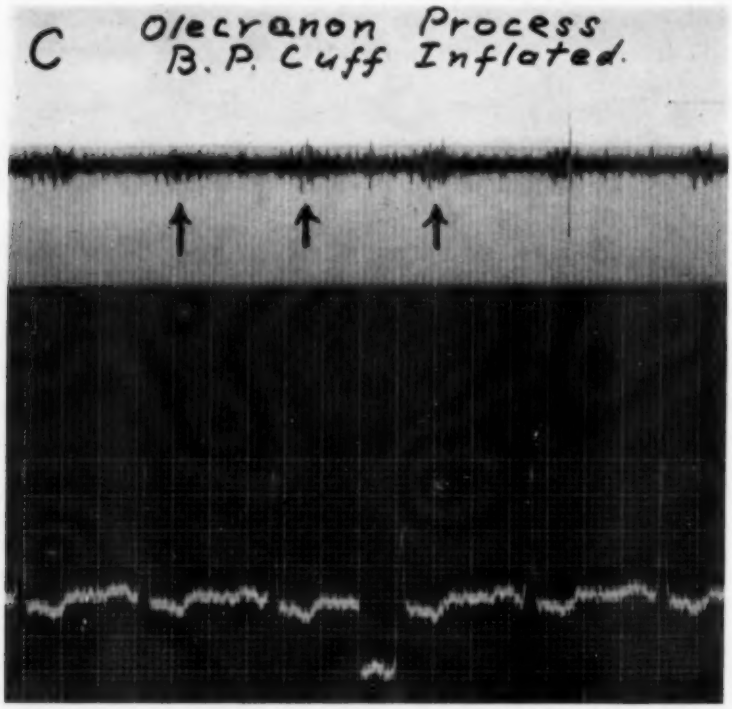


FIG. 1, C. Record C was also from the right elbow, but with the blood pressure cuff inflated to 220 mm. (patient's pressure was 160/80). Note persistence of systolic murmur (arrows). (Cambridge Instrument Co. machine.)

does take place occurs "in" and not "with" the blood stream and would be distributed equally both against and in the direction of the blood flow. It has even been thought that a systolic murmur heard over the aortic area and also over the carotid artery was much more likely due to aortic stenosis than if it were not heard in the neck. Likewise, an apical systolic murmur that was well heard in the axilla would have a greater value in indicating mitral insufficiency than if it were not transmitted in this fashion. The contention that we wish to maintain is that a loud aortic systolic murmur will be heard in the neck because it is near the neck, and a loud apical murmur will be audible in the axilla for the same reason. It should follow that a very loud pulmonary systolic murmur, or any grade 5 or 6 murmur, ought to be audible in the carotid region. That this is true will be seen below. In general, we feel that a murmur is transmitted in all directions from the point of maximum intensity, and that once the sound strikes bone it is best transmitted through contiguous bony structures. At first this idea was merely a suspicion, but, when, for many years, loud systolic murmurs were detected over the olecranon process with the ordinary bell stethoscope, it became more of a conviction. Finally, it might have been maintained that a systolic murmur present over the bony process of the elbow was still transmitted from a neighboring blood vessel. This possibility was eliminated when the sound

remained audible even after pressure, above the level of the systolic blood pressure of the patient, was maintained proximal to the olecranon process.

Figure 1 was obtained in the case of a woman, aged 38, with marked aortic stenosis having a loud, grade 6, aortic systolic murmur. Record A was taken from the aortic area and shows a loud systolic murmur. Record B was obtained with the microphone over the olecranon process of the right

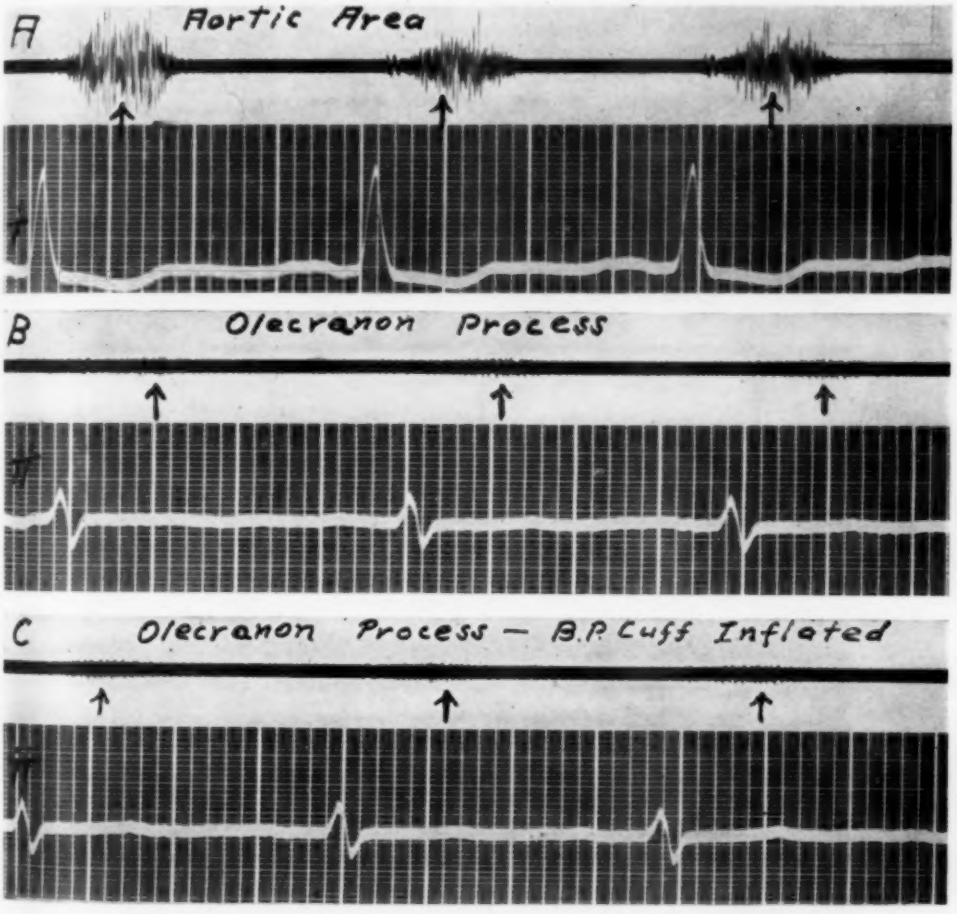
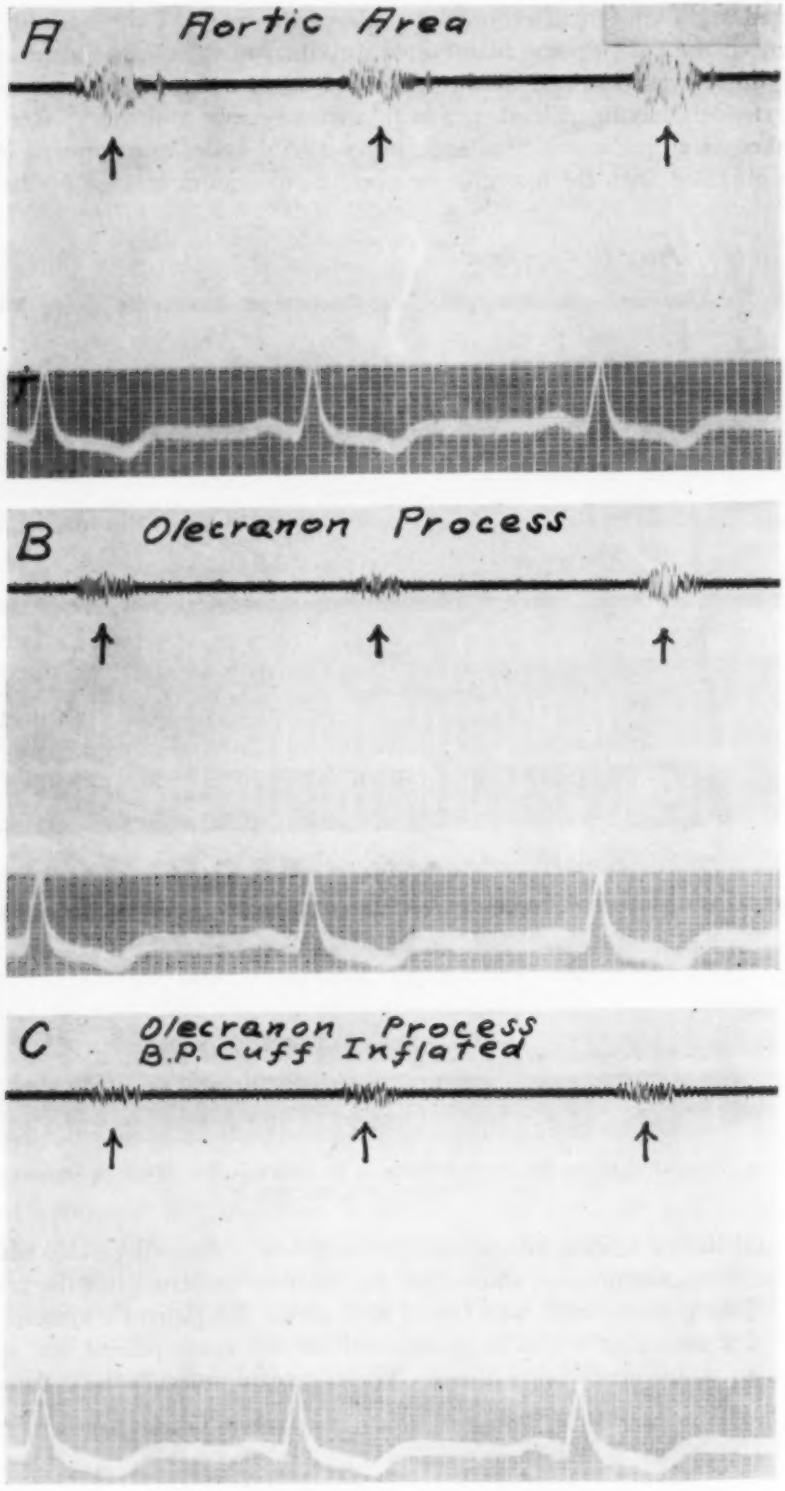


FIG. 2. Similar data on the same patient as in figure 1, but obtained six months later. (Sanborn Co. machine.)

elbow and shows definite vibrations late in systole. Record C, also obtained from the olecranon process, shows that the murmur persists after the pressure in the blood pressure cuff was raised well above the patient's systolic level. Figure 2 shows similar findings obtained on the same patient six months later with a different apparatus.* With careful auscultation, using the

*We wish to thank M. B. Rappaport, E.E., of the Sanborn Co., for some advice in this work.


A
Aortic Area
B
Olecranon Process
C
Olecranon Process
B.P. Cuff Inflated

ordinary stethoscope, these faint, clearly detectable, systolic murmurs have been heard over the elbow in many different cases. Another instance is very clearly illustrated in figure 3, obtained from a woman aged 44 with marked aortic stenosis.

In these two cases systolic murmurs were transmitted very widely through bone. In the following instance (figure 4) a very loud, musical, grade 6, aortic diastolic murmur was present in a man about 50 years of age with syphilitic aortic insufficiency. It was suspected that this patient ruptured an aortic cusp, for, after a sudden, violent strain, he first became aware of a noise in his chest. Here the blood flow producing the murmur was taking place from aorta into the left ventricle during diastole. Despite this, the murmur was readily heard, widely distributed and easily detected at the top of the skull and over the olecranon process.

If the transmission of a murmur primarily depends upon its intensity, then it should follow that a murmur that is very loud over the base of the heart, produced in the pulmonary valve or in some other area, such as a defect in the interventricular septum, ought to be detectable in the region of the carotid artery, just as occurs in cases of aortic stenosis. Figure 5 shows that this supposition is true. This patient was a young man of 23, known to have a heart murmur since birth, showing definite evidence of an interventricular septal defect (Roger's disease). He had a grade 6 systolic murmur best heard over the mid-precordium, and there was right bundle branch block in the electrocardiogram. The murmur was very loud over the pulmonary area, as shown in the first several beats of record A (figure 5). The transmission of the murmur to the neck is clearly indicated in record B. A similar mechanism is illustrated in figure 6. This woman, aged 29, had classical signs of tetralogy of Fallot. There was a grade 5 systolic murmur in the pulmonary area due to pulmonary stenosis (figure 6, record A). This murmur was also clearly audible over the carotid artery (record B). It must be appreciated that in the first of these two cases the flow of blood producing the murmur was from left ventricle to right ventricle through the septal defect, and in the second instance was from right ventricle through a stenosed pulmonary valve into the pulmonary artery. The presence of the murmur in the carotid artery, therefore, can not be accounted for by the flow of blood through the aorta, but must be transmitted from its origin within the right ventricle on the one hand, and the pulmonary artery on the other.

In evaluation of a systolic murmur it is common practice to have the patient exercise, or to observe the effect of breathing on the murmur. In a previous communication [2] it was clearly established that most normal adults develop a grade 1 to grade 2 apical systolic murmur directly after a brisk

FIG. 3. Simultaneous phonocardiograms and electrocardiograms on a woman 44 years of age with marked aortic stenosis. Record A shows coarse systolic murmur (arrows) at aortic area. Record B shows systolic murmur detected at olecranon process (arrows), and record C shows the same murmur (arrows) with blood pressure cuff inflated to 220 mm. (patient's blood pressure was 158/60).

effort. It is likewise true that a slight systolic murmur can become accentuated after such effort. Figure 7 was obtained from a 24 year old medical student with no evidence whatever of cardiac disease. Record A shows the absence of any murmur at the apex of the heart. Record B was taken within 30 seconds after a period of brisk exercise and depicts the fine systolic murmur heard at the apex and classified as grade 1. No diagnostic conclusion, therefore, can be drawn from the detection of a systolic murmur that is produced by exercise.

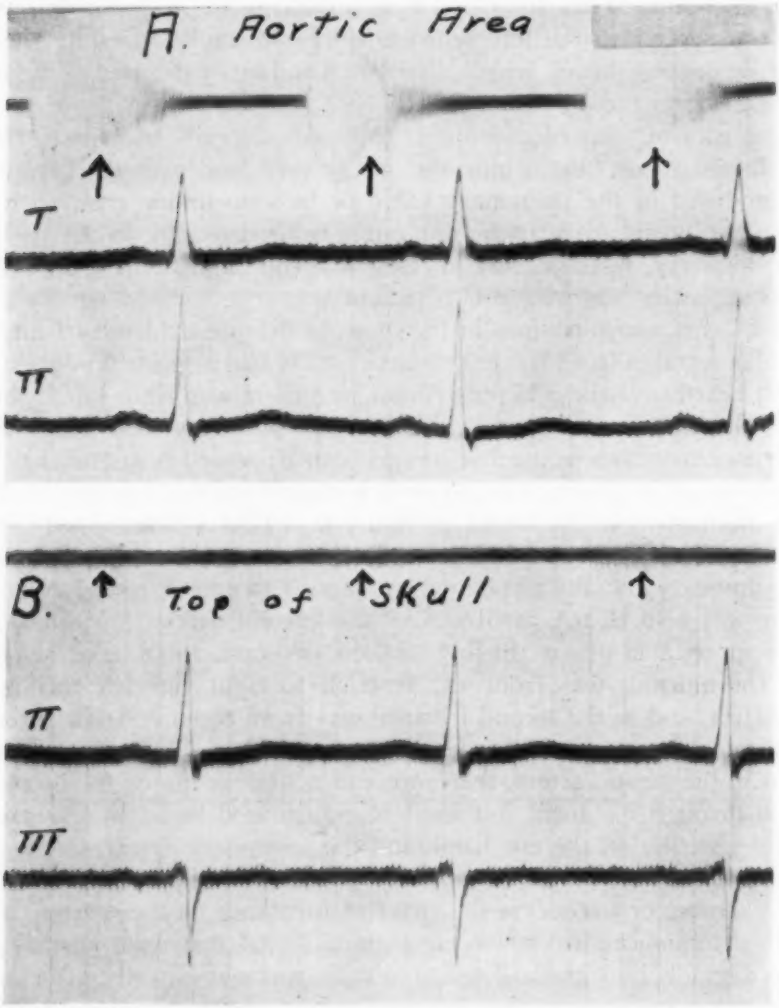


FIG. 4, A and B. Simultaneous phonocardiograms and electrocardiograms on a man about 50 years of age with syphilitic aortic insufficiency with possible ruptured aortic valve. There was a grade 6 musical aortic diastolic murmur. Record A shows fine diastolic murmur (arrows) in aortic area. Record B shows faint diastolic murmur (arrows) obtained from top of skull.

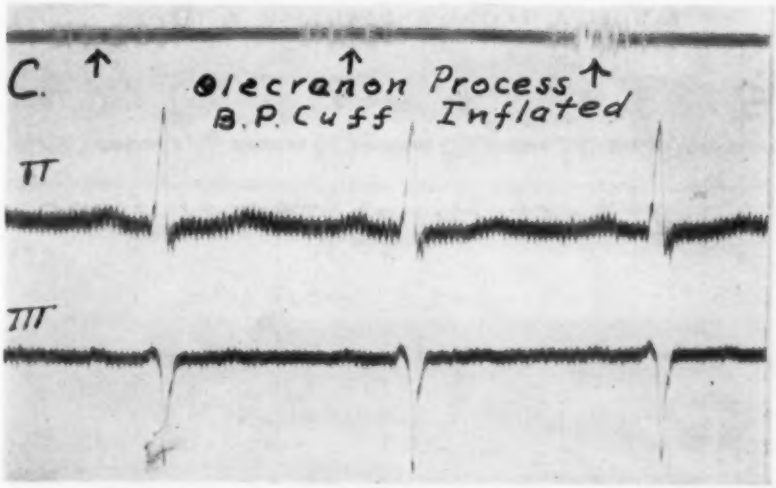


FIG. 4, C. Record C shows moderate diastolic murmur (arrows) from olecranon process with blood pressure cuff inflated to 220 mm. (patient's blood pressure was 140/60). (Courtesy of Drs. Henry H. Haft and Jane Sands Robb of Syracuse, N. Y.)

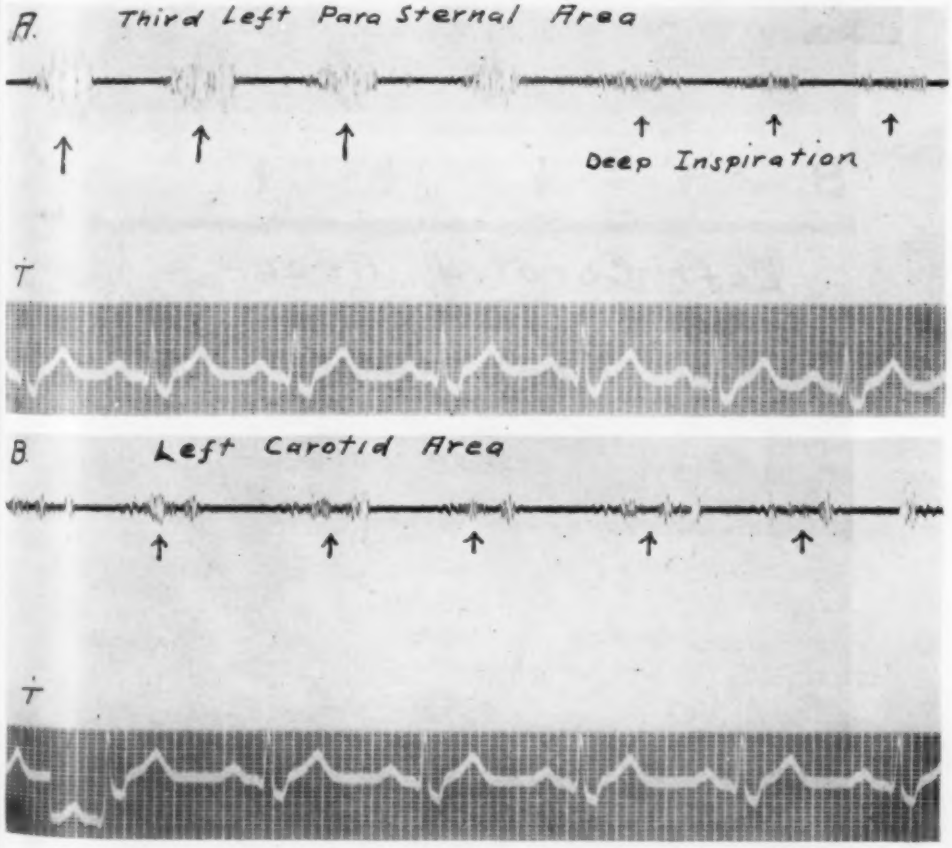


FIG. 5. Simultaneous phonocardiograms and electrocardiograms on a young man of 23 with interventricular septal defect. Record A was taken from the third left parasternal area and shows a loud systolic murmur (arrows) which, after several cycles, becomes faint on taking a deep inspiration. Record B, obtained from the left carotid area, shows definite, moderate systolic murmur (arrows).

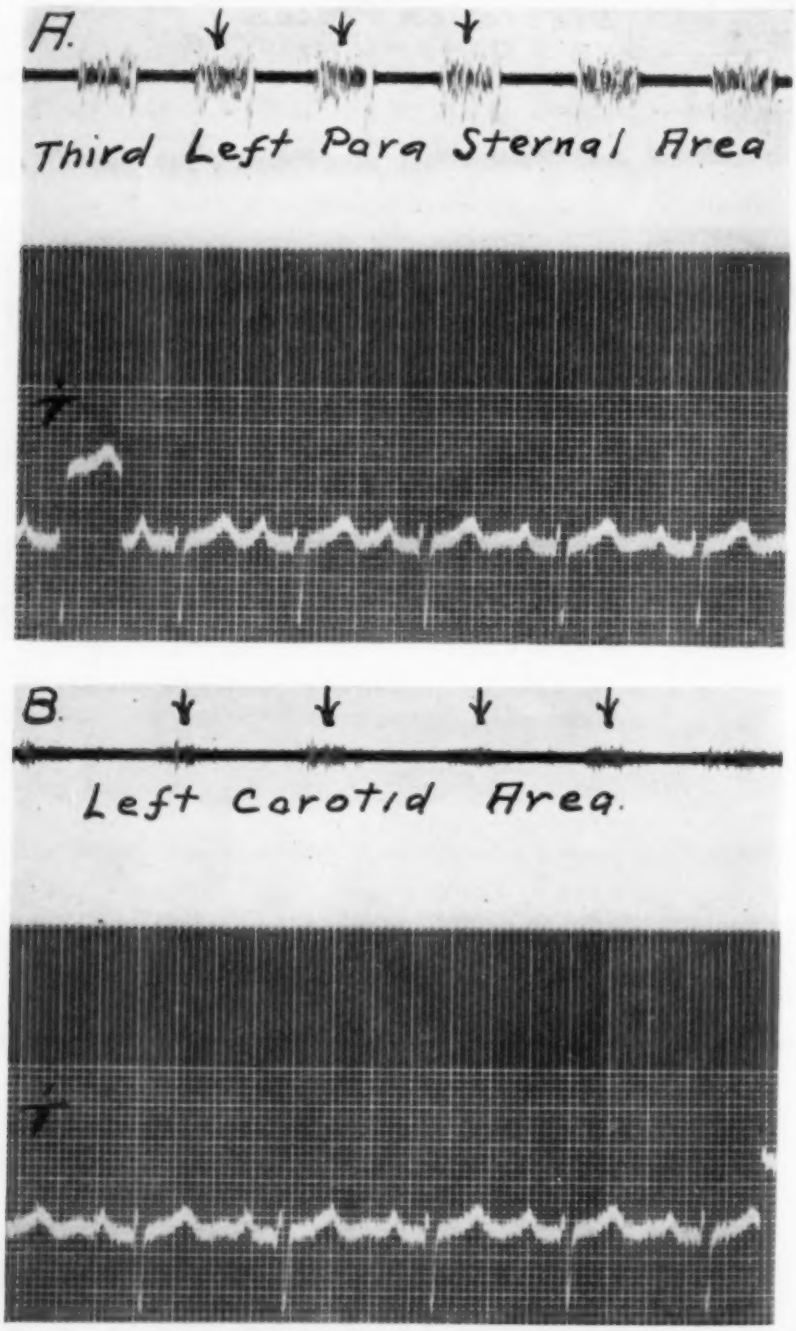


FIG. 6. Simultaneous phonocardiograms and electrocardiograms on a woman, aged 29, with tetralogy of Fallot. Record A, from third left parasternal area, shows loud systolic murmur (arrows). Record B, from upper left carotid area, shows definite, moderate systolic murmur (arrows).

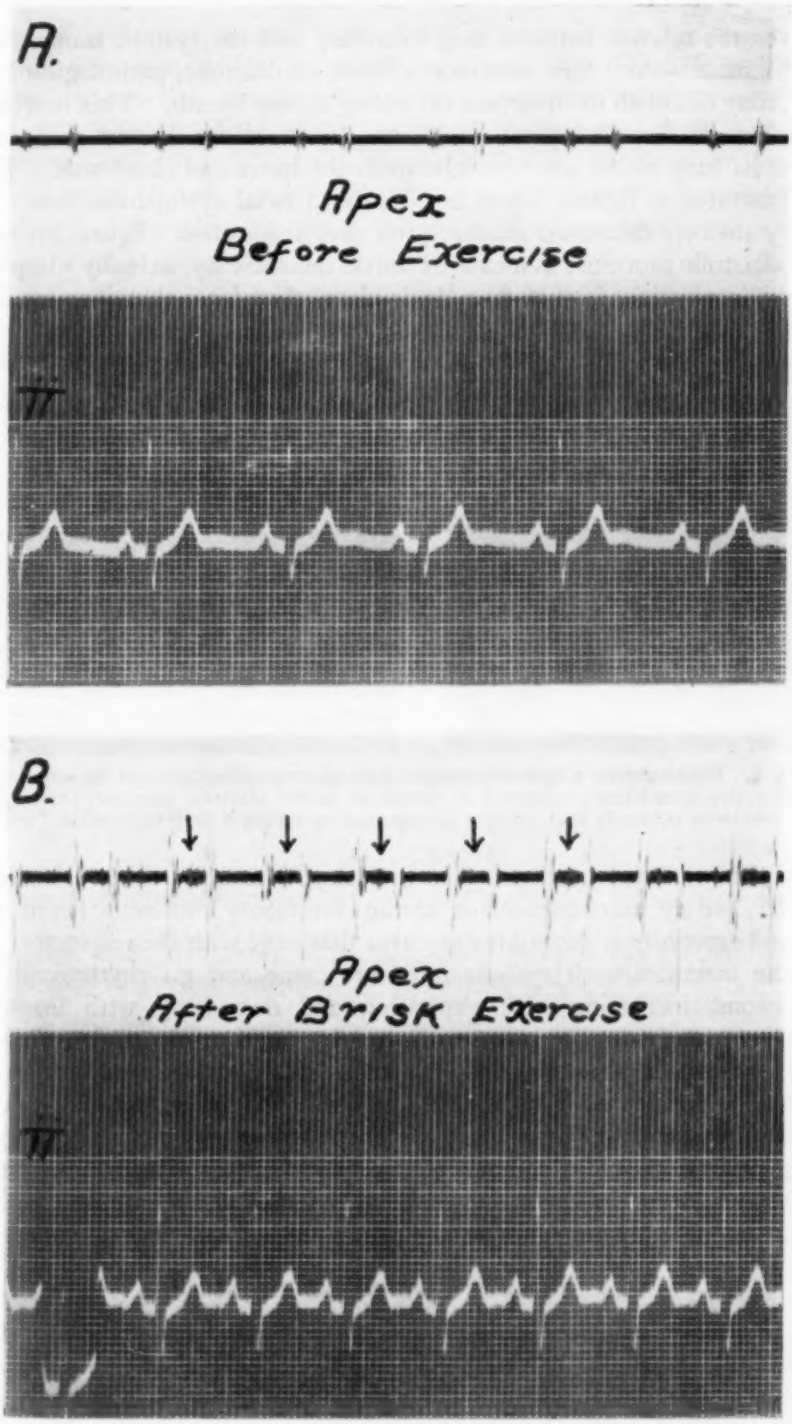


FIG. 7. Simultaneous phonocardiograms and electrocardiograms on a medical student of 24 with no heart disease. Record A, taken at the apex, fails to show any murmur. Record B, taken within 30 seconds after a period of brisk exercise, shows a fine systolic murmur (arrows) which was clearly heard at the apex and classified grade 1.

Even the relation between deep breathing and the systolic murmur is no simple matter. Any faint murmur, systolic or diastolic, pathologic or functional, may diminish or disappear on taking a deep breath. This is what one might expect, for all heart sounds can become more distant as a greater amount of lung tissue intervenes between the heart and chest wall. This is well illustrated in figures 5 and 8. The loud basal systolic murmur of pulmonary stenosis decreased markedly on deep inspiration (figure 5), and an aortic diastolic murmur, in a case of aortic insufficiency, actually disappeared on deep inspiration (figure 8). It is clear, therefore, that intracardiac or

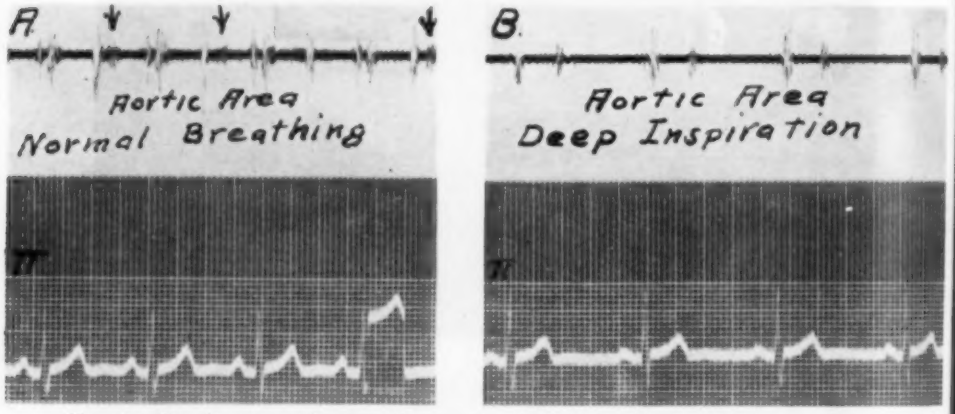


FIG. 8. Simultaneous phonocardiograms and electrocardiograms on a young man of 26 with aortic insufficiency. Record A shows an aortic diastolic murmur (arrows) with patient breathing normally that entirely disappeared on taking a deep inspiration (record B).

endocardial murmurs can vary in intensity with respiration. There are, however, purely extra-cardiac or cardio-respiratory murmurs heard at the apex and especially at the pulmonary area that vary with the respiratory cycle. In some instances such systolic murmurs come and go rhythmically with respirations, increasing with expiration and decreasing with inspiration. We have a suspicion that some cardio-respiratory systolic murmurs are only present at certain phases of inspiration, as if the cushion of lung receives the systolic impact with each beat. In other instances, especially in thin-chested individuals, the pulmonary systolic murmur may be present only with a deep expiration. May this not be due to the actual impact of the pulmonary artery against the chest wall? It is obvious that the simple question of the relation of heart murmurs to respiration needs further investigation.

SUMMARY AND CONCLUSIONS

1. Numerous simple questions concerning the production and propagation of murmurs remain unanswered.

2. We believe that the velocity of blood flow through the cardiac chambers and great vessels is one important factor in the production of murmurs and in determining their intensity.

3. Other factors, such as the amount of residual blood in cardiac chambers, the proximity of the heart and great vessels to the chest wall, and the respiratory cycle may influence the presence or absence of murmurs.

4. We believe that the gradation of systolic murmurs from 1 to 6 is important in attempting to estimate their significance, for those of grade 3 intensity, or louder, are never observed in normal individuals, whereas those of grade 1, and occasionally grade 2, are found where there is no evidence of cardiac or other disease.

5. The detection of murmurs over the olecranon process even with the blood pressure cuff inflated above the systolic pressure level, proves that murmurs are transmitted through bone.

6. The transmission of an aortic diastolic murmur to the skull, and of the systolic murmur of ventricular septal defect to the carotid area proves that murmurs are not propagated with the blood stream, for the blood flow in these circumstances is in the opposite direction.

7. Systolic murmurs after effort occur in normal individuals. The production or accentuation of such murmurs after exercise, therefore, can not be used as a diagnostic test.

8. There are several mechanisms involved when murmurs are influenced by respiration. All faint murmurs, organic or functional, may disappear with a deep inspiration. In some instances extracardiac systolic murmurs may be louder, and in others fainter, with a deep expiration.

9. The current teaching about propagation of murmurs needs revision.

10. These considerations are important in the examination of selectees for military service.

BIBLIOGRAPHY

1. Levine, S. A.: The systolic murmur: its clinical significance, Jr. Am. Med. Assoc., 1933, ci, 436–438.

2. Freeman, A. R., and Levine, S. A.: The clinical significance of the systolic murmur: A study of 1000 consecutive non-cardiac cases, Ann. Int. Med., 1933, vi, 1371–1385.

CASE REPORTS

PATENT DUCTUS ARTERIOSUS WITH PULMONARY VASCULAR SCLEROSIS AND CYANOSIS *

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Patent ductus arteriosus is a congenital cardiac lesion usually producing a shunt of blood from the aorta to the pulmonary artery. Cyanosis in the condition is rare, although a transient cyanosis may sometimes be seen following bouts of crying or coughing.[1] Maude Abbott states that the left ventricle is characteristically more enlarged than the right, but a recent report by Keys and Shapiro [2] indicates that the reverse may be true. Pulmonary vascular sclerosis and polycythemia are not components of the syndrome as usually described. The following case of patent ductus arteriosus is remarkable in that (a) there was cyanosis of at least five years' duration, (b) there was a striking degree of right ventricular hypertrophy, (c) pulmonary vascular sclerosis was advanced, and (d) secondary polycythemia was consistently found.

Case Report

A 37 year old married taxi driver was admitted to the Boston City Hospital on January 30, 1943 for the tenth time.

He stated that when 12 years old he had had an attack of rheumatic fever. He was accepted for life insurance at the age of 14 but was refused further insurance at the age of 26 because of a "heart murmur." In March, 1936, at the age of 30, he visited the Out Patient Department complaining of increasing dyspnea on exertion for one year. His heart was enlarged, the left border being 11.5 cm. from the midline in the fifth left interspace, and a low-pitched diastolic murmur was heard in the third and fourth left interspaces 4 cm. from the midline. The diagnosis at that time was rheumatic heart disease with mitral stenosis.

He was admitted to the hospital in December, 1938, complaining of breathlessness, cough and bloody sputum for one day. On physical examination the patient was very plethoric and cyanotic about the face and lips. Venous engorgement was absent. The AP diameter of the chest was slightly increased, and there were a few moist râles at the base of the left lung. The heart size and murmurs were the same as recorded two years previously. Neither the liver nor the spleen was felt. The blood pressure was 140 mm. Hg systolic and 95 mm. diastolic in the arms and in the legs. The urine contained small amounts of albumin. The hemoglobin varied between 21 and 25.7 grams per 100 c.c. blood (Sahli). The red cell count varied between 6 and 7 million per cu. mm. The white cells were within normal limits in number and types. The hematocrit varied between 60 and 74.5 per cent. Five sputum examinations were negative for tubercle bacilli. The venous pressure in the right arm was 6 cm. of

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From the Thorndike Memorial Laboratory, the Second and Fourth (Harvard) Medical Services and the Mallory Institute, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

water. Arterial oxygen saturation was 75 per cent. An electrocardiogram showed right axis deviation. The discharge diagnoses were congenital heart disease with pulmonary insufficiency and patent interauricular septum.

Between the first entry in 1938 and the final entry in 1943, the patient was admitted eight times complaining variously of dyspnea on exertion, small hemoptyses and swollen, painful joints. The hemoglobin and red cell count were always in the neighborhood of 18 grams per 100 c.c. of blood (Sahli) and 8 million per cu. mm., respectively. Venesections were carried out approximately 20 times, 500 to 600 c.c. being removed each time with considerable symptomatic relief. A systolic murmur was regularly heard in the fourth left interspace, but the previously reported diastolic murmur was infrequently heard. Arterial oxygen saturation values during 1940 and 1941 varied between 89 and 94 per cent. Fluoroscopic and roentgenographic examinations at various times during this period demonstrated marked general enlargement of the heart and a prominent pulmonary conus. The right ventricle was considerably enlarged and hyperactive, whereas the left auricle appeared normal.

While a patient at the Peter Bent Brigham Hospital in 1942 the heart size and murmurs were found to be the same as originally noted, although the diastolic murmur was not heard by all observers. The effect of oxygen administration on arterial oxygen saturation was studied in Dr. C. Sidney Burwell's laboratory and the following results obtained:

Before oxygen administration	82 per cent saturated
After 30 minutes' exposure	100 per cent saturated
10 minutes after stopping oxygen	97 per cent saturated
Vital capacity	3.5 liters

Five days before the tenth and last admission to the Boston City Hospital, the patient noted pain on the dorsum of the left foot followed after 12 hours by hemoptysis and sharp pain in the left lower chest. The hemoptysis and chest pain did not recur, but the pain in the left foot continued, ultimately causing him to seek hospitalization.

On physical examination the temperature was 98.6° F., the pulse rate 90, and the respiratory rate 24. The blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. The plethoric, cyanotic appearance noted in 1938 was still present. There was no venous engorgement, and the lungs were entirely clear. The heart was enlarged 12 cm. to the left of the midsternal line and there was a rough apical systolic murmur. No diastolic murmur was heard. P2 was louder than A2. The liver was felt three fingers' breadth below the costal margin. Both great toes were red, cyanotic and tender to motion, but the temperature of the affected joints was normal. Dorsalis pedis and posterior tibial arterial pulsations were bilaterally palpable. The veins of the legs were not palpable, and there was no calf tenderness.

Significant laboratory data included a hemoglobin of 16.4 grams per 100 c.c. blood (Sahli), a red cell count of 7.6 million, and a white cell count of 6800 per cu. mm. All urine specimens contained rare red cells, granular casts and moderate amounts of albumin. An electrocardiogram showed marked right axis deviation.

On the second hospital day a venesection of 500 c.c. was performed. Later in the day it was decided, largely on the basis of the history, that the patient had a thrombosis of the veins of his leg, giving rise to pulmonary infarcts. Femoral ligations were advised by the surgical consultants and the operation was performed about 48 hours after admission. While in the operating room, the patient suddenly became very dyspneic and cyanotic. He responded to the administration of oxygen, caffeine and coramine but on return to the ward again became very dyspneic. Oxygen and various restoratives were given, but in spite of these measures he gradually became comatose and died 12 hours after the operation. Discharge diagnoses were congenital

heart disease with interauricular septal defect, secondary polycythemia and pulmonary infarcts.

Postmortem Examination. Externally the body was that of a normally developed, well-nourished adult male, appearing considerably older than his stated age of 37 years. There was a patchy cyanosis of the face, neck and shoulder girdle.

FIG. 1. View of the right side of the heart showing from below above, greatly thickened right ventricle, healed pulmonic endocarditis, dilated pulmonary artery with its main branches and widely patent ductus surrounded by many atheromatous plaques.

There were bilateral recent healing skin incisions over the femoral veins, each 10 cm. in length. There was only slight edema over the dorsum of the left foot. There was a slight precordial bulge but no clubbing of the fingers or toes.

The peritoneal cavity was without pathologic change. Pleural and pericardial cavities contained normal amounts of clear, serous fluid. The heart was enlarged,

weighing 680 grams, and anteriorly was composed almost completely of the right ventricle so that the left ventricle appeared to be an appendage to the preponderant right ventricle. The epicardium was essentially negative. The myocardium of

FIG. 2. Large artery showing in right lower field an asymmetrical internal atheroma with fibrous internal proliferation. Verhoeff. elastic tissue stain × 40.

the right ventricle was greatly increased in thickness, varying from 1.8 to 2.2 cm., in striking contrast to the essentially normal left ventricle with a thickness of 1.4 cm. The right atrium was dilated and there was slight dilatation of the right ventricle.

The tricuspid and pulmonic valve rings were similarly dilated to 15.0 and 11.0 cm., respectively. The leaflets of all the valves, with the exception of the anterior cusp of the pulmonic valve, were thin, translucent and flexible with no evidence of atherosclerosis or fibrous thickening of intercommissural adhesions. The anterior leaflet of

FIG. 3. Medium-sized artery with fairly marked intimal atherosclerosis; thrombosis and recanalization of lumen. Verhoeff. elastic tissue stain × 50.

the pulmonary valve presented at the mid-point of its base a heaped-up, irregular, mulberry-like calcific mass measuring 1.5 by 1.0 by 0.5 cm. These calcified vegetations were everywhere smooth and glistening and were completely covered with endothelium. They penetrated the leaflet and protruded within the sinus of Valsalva.

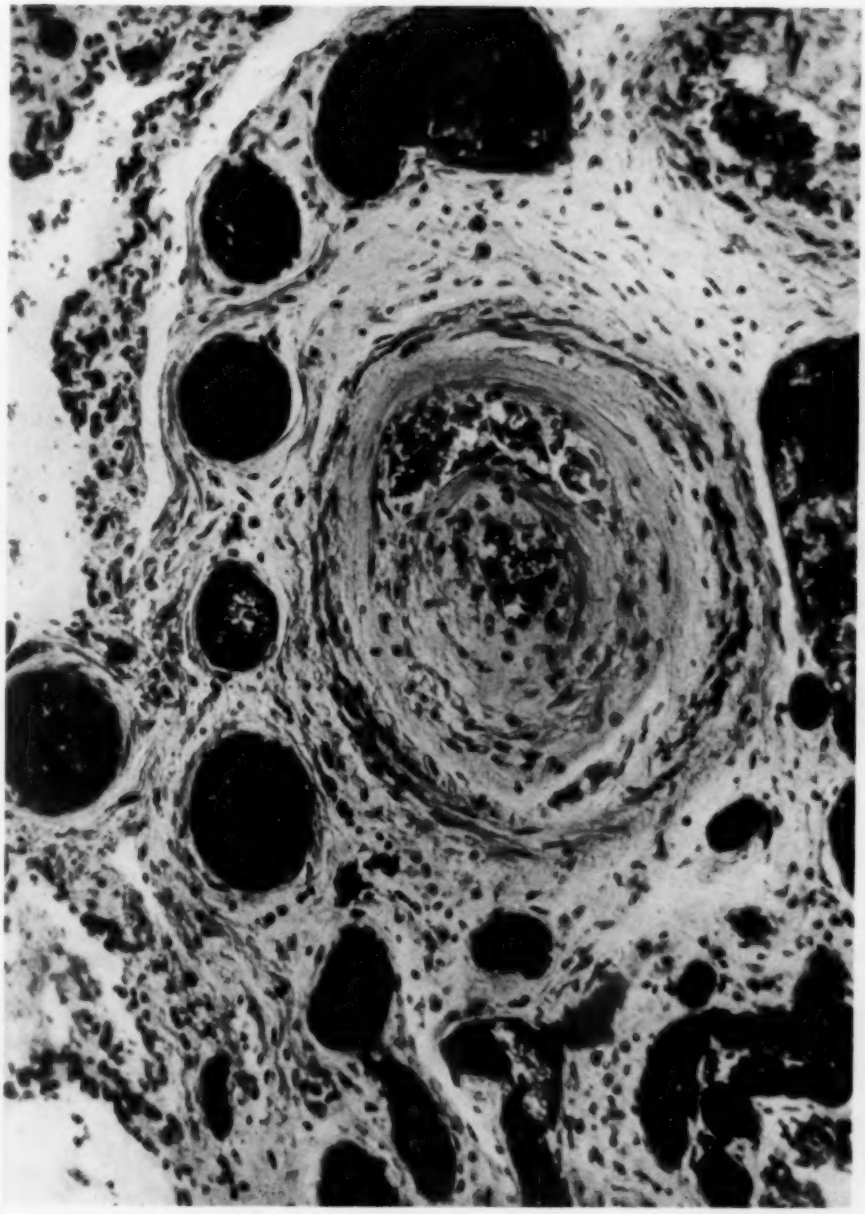

FIG. 4. Small artery of lung showing hyperplastic endarteritis with narrowing of lumen. Phloxine-methylene blue stain × 150.

Attached to this basal mass and extending to the free margin of the valve cusp was a thin subendocardial calcific plaque which made the cusp stand out rigidly from the wall. The main pulmonary artery was moderately dilated to a maximum of 12 cm. in circumference. It contained a marked amount of calcific atherosclerosis. There was a widely patent ductus arteriosus 8 cm. distal to the pulmonary valve ring at

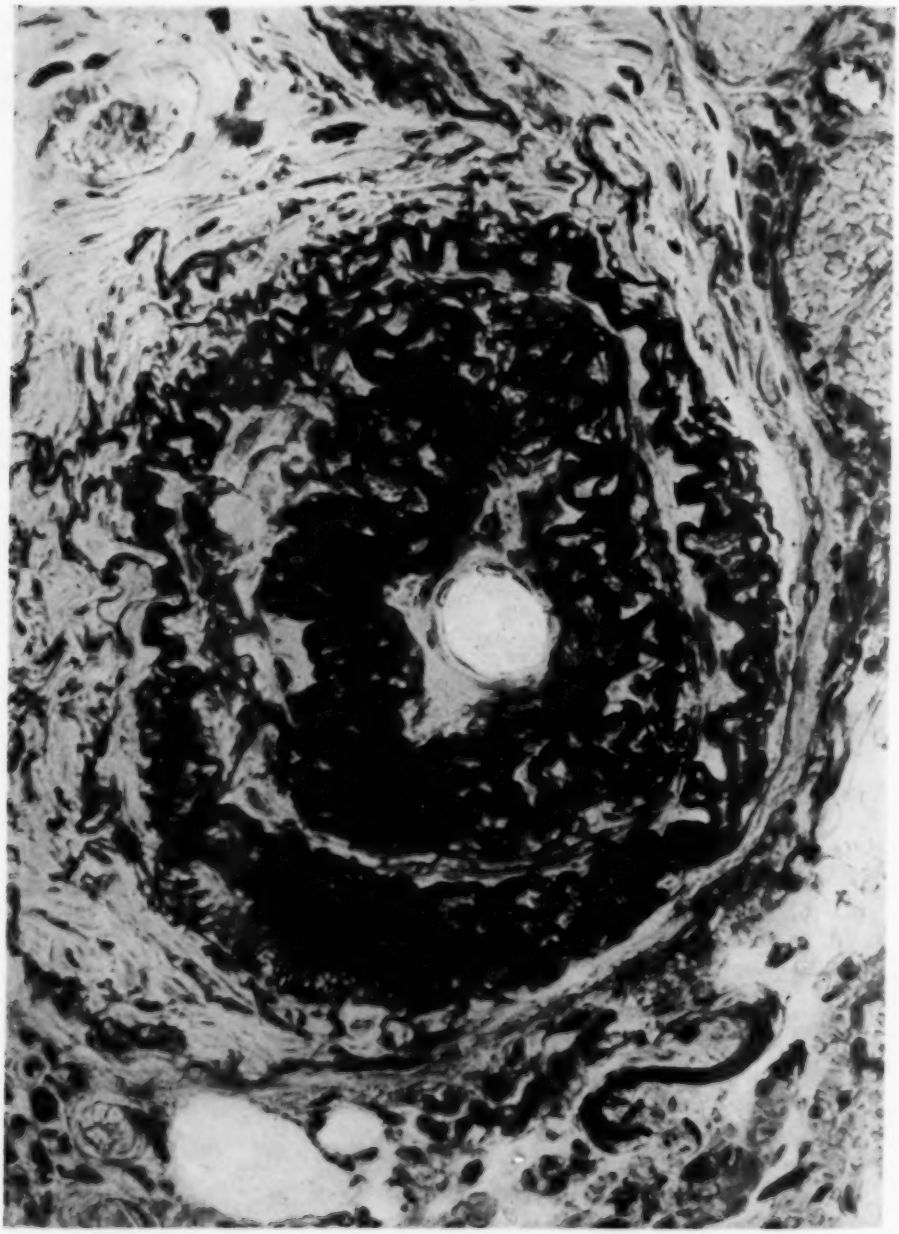

FIG. 5. Small artery showing marked thickening and tortuosity of elastica interna with a similar, but less dominant, change in the externa. Verhoeff. elastic tissue stain × 500.

the point where the pulmonary artery is in direct apposition to the aorta. It was roughly circular in outline with a diameter of 1.2 cm. and its opening in the wall of the pulmonary artery was surrounded by a large calcification (figure 1). The ductus consisted of a simple opening connecting the lumina of the great vessels. No calci-

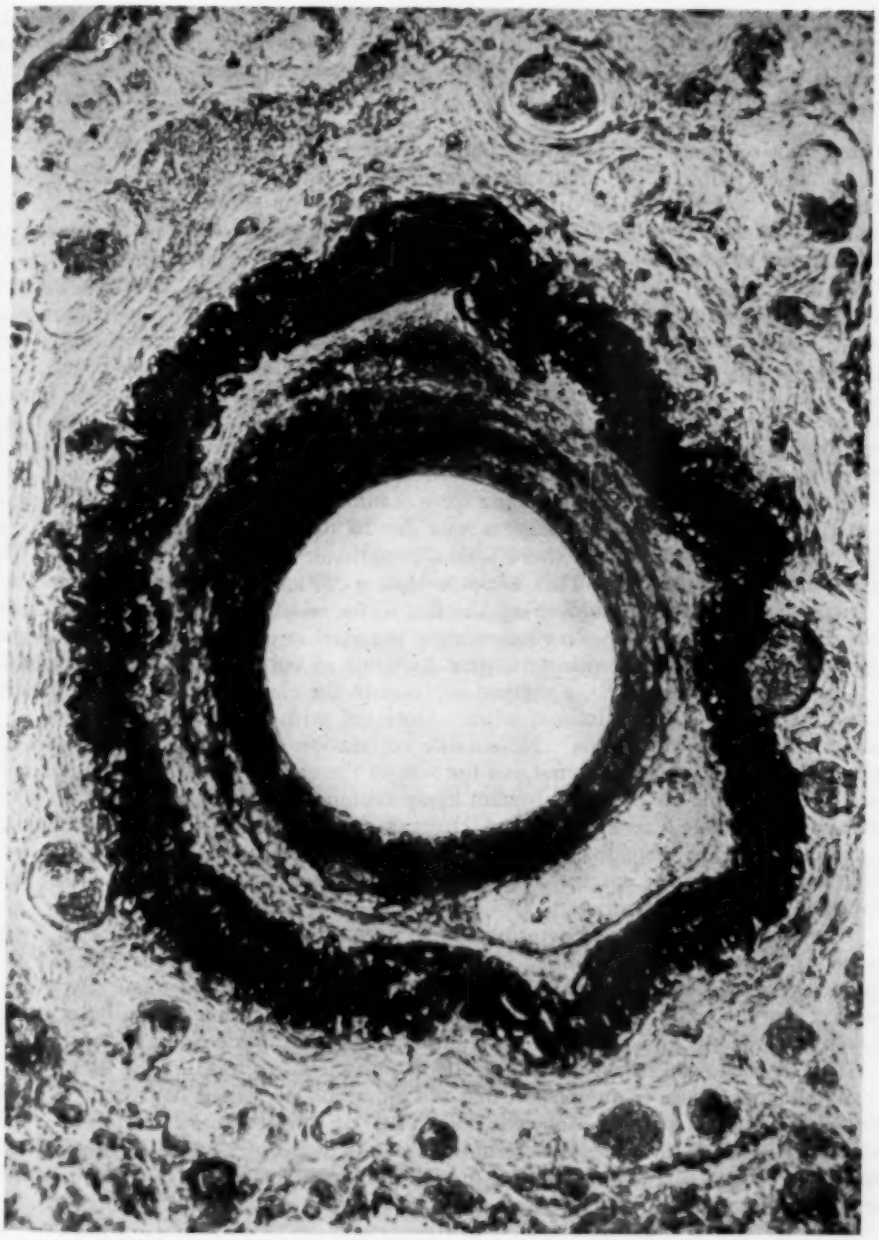

FIG. 6. Medium-sized artery showing destruction of a well-defined elastica interna, diffuse increase in elastic tissue within intima and media; thickening and re-duplication of elastica externa. Verhoeff. elastic tissue stain × 200.

fied vegetations were seen about the margin of the ductus save for the described atherosclerosis.

The lungs were essentially negative grossly, each weighing 340 grams and containing no definite evidence of infarction or hemorrhage. The pulmonary arterial

tree, while containing no emboli, showed diffuse thickening of the walls of all the grossly visible vessels so that on cut section they protruded above the parenchymal surface in "pipe-stem" fashion. The spleen and liver were moderately enlarged. The two kidneys weighed 460 grams and except for the slight increase in their size and weight were grossly negative. The veins of the legs were explored down to the ankles and were entirely patent except at the points of operative ligature. The brain showed no pathologic change. The anatomical diagnoses were: (*a*) congenital heart disease, patent ductus arteriosus, healed pulmonic endocarditis, cor pulmonale (marked), (*b*) pulmonary atherosclerosis, (*c*) right-sided cardiac decompensation as evidenced by splenomegaly and hepatomegaly.

Microscopically, the only findings of interest were in the lungs, liver and kidneys. The lungs showed no microscopic evidence of recent infarction. The alveolar spaces were entirely clear except for a slight amount of amorphous, albuminous precipitate in the basal portion of both lower lobes. Of greatest interest were the arteries which showed in the larger branches thickening of the walls by far advanced intimal atherosclerosis, which in one vessel had led to thrombosis of the lumen with subsequent organization and recanalization (figures 2 and 3). The medium-sized elastic arteries and smaller muscular arteries showed relatively greater thickening of their walls so that in certain areas the lumina were diminished to fine capillary-like channels (figure 4). The increase in thickness was due to fibrous intimal proliferation. In addition to the above findings there was a remarkable increase in the elastic tissue content of all the arteries. This increase took a variety of forms. In some vessels it consisted in great thickening chiefly of the elastica interna with relatively little change in the externa. In other vessels, the externa appeared to have undergone reduplication and splitting with no apparent change in the interna (figures 5 and 6).

Throughout most vessels, a marked increase in the elastic fibrils could be demonstrated in the media and intima, often associated with complete destruction of a clearly defined elastica interna. No definite correlation could be drawn between the type of elastic tissue change found and the size of the vessel. Study of representative samples of systemic vessels in malignant hypertension and pulmonary vessels in mitral stenosis demonstrated no elastic tissue changes comparable with the above findings. Phosphotungstic acid-hematoxylin stains revealed no significant abnormality within the media or adventitia, except for a slight increase in perivascular fibrous tissue with dilatation of the vasa vasorum.

The smallest arteries and arterioles were normal, showing no evidence of hyperplastic or necrotizing arteriolitis. At the bases of both lower lobes the alveolar capillaries showed moderate dilatation with some reduplication and tortuosity of their courses. In the main, however, the alveolar walls were unlike those described by Parker and Weiss,[8] and presented only minimal intramural edema and fibrosis.

The liver showed marked acute hemorrhagic central necrosis of the lobules.

The kidneys were of interest in that the glomeruli presented increased cellularity due to endothelial proliferation with splitting of the basement membrane. The picture was considered to be consistent with a late stage of acute diffuse glomerulonephritis. No vascular changes were found elsewhere in the body. The heart presented no microscopic evidence of an earlier rheumatic involvement.

Discussion

In the light of the preceding pathologic data it seems possible to correlate to some extent the findings of patent ductus arteriosus, pulmonary vascular sclerosis, right ventricular hypertrophy, and cyanosis.

Normal blood pressures in the pulmonary arterial tree are considered by standard textbooks to approximate one-sixth of systemic blood pressure values.

Hence, in the usual case of patent ductus arteriosus, the shunt must be from left to right. In addition, Burwell and colleagues [4] have shown by animal and clinical experimentation that as much as 40 to 75 per cent of the total left ventricular output may pass through a patent ductus, depending upon the size of its lumen. Inasmuch as the patient under consideration had a widely patent ductus it seems reasonable to infer that large amounts of aortic blood were added to the pulmonary circulation. This increase in pulmonary blood volume must have created initially a slight pulmonary hypertension which became severe as a later result. The latter manifested itself in a fashion exactly analogous to systemic hypertension, namely by ventricular hypertrophy and vascular sclerosis; in this case by hypertrophy of the right ventricle and sclerosis of the pulmonary arterial tree. A similar thesis, namely that the vascular changes constitute a "physiopathologic response to pulmonary hypertension," has been suggested in connection with *primary* pulmonary vascular sclerosis by Brill and Krygier.[5] The vascular changes, as has been pointed out, are of the secondary type,[6] being prominent within the larger branches of the pulmonary artery and practically negligible within the smallest arteries and arterioles. The most common conditions producing elevated pulmonary pressures, e.g., left ventricular failure and mitral stenosis, place a strain initially on the pulmonary veins and capillaries. Since these portions of the pulmonary vascular system are highly distensible, effects of the increased pressure may be very late, and although capillary changes may be seen microscopically, there is usually little or no pulmonary arterial change, consisting, when present, of atherosclerosis in the larger vessels. In our case, however, the shunting of large amounts of arterial blood directly into the pulmonary artery produced pronounced pulmonary arterial changes with minimal capillary and venous changes.

The etiology of the cyanosis observed in the patient after 1938 is obscure. Three independent or combined possibilities present themselves:

(1) Entrance of venous blood into the systemic circulation via the patent ductus arteriosus.
(2) Peripheral venous stagnation.
(3) Pulmonary vascular changes.

In regard to the first possibility, it seems unlikely that the pulmonary hypertension ever reached such levels as would create a right to left shunt except possibly as a terminal event. Relative to peripheral venous stagnation, it is noteworthy that there was never clearly defined clinical evidence of congestive failure. However, the pathologic findings of right ventricular hypertrophy and dilatation, and hemorrhagic necrosis of the liver indicate that some degree of right ventricular decompensation must have been present. In addition, "in a subject with an abnormally high blood count a degree of slowing of the peripheral blood flow which would be without effect upon a person possessing a normal hemoglobin content will result in cyanosis." [7] This is, of course, only an "appearance." Actually, the per cent of unsaturation for a given loss of oxygen will be less in polycythemia. That pulmonic factors were of some significance is supported by the oxygen saturation tests carried out in Dr. Burwell's laboratory, which indicated that exposure of the patient to 80 per cent oxygen raised the saturation of the arterial blood from 82 to 100 per cent. This result is inconsistent with the passage of venous blood directly into the arterial circulation and suggests that the passage

of oxygen from the alveoli to the red blood cells may have been impaired. On the basis of these data it was Dr. Burwell's opinion that while the patient was at rest there was no shunting of blood from right to left. He felt that the cyanosis was pulmonic in origin and suggested that a left to right shunt might impose a burden on the pulmonic circulation and result in a "progressive pulmonary abnormality." The relationship of pulmonary sclerosis to cyanosis is not clear. The sclerotic process involved the larger elements of the pulmonary arterial tree, and did not affect per se the alveoli or alveolar capillaries, the actual sites of oxygen transfer. Cyanosis was present in 17 per cent of the cases of secondary pulmonary vascular sclerosis collected by Brenner.[6] He doubted, however, that there was any relation between pulmonary vascular sclerosis and the production of cyanosis. The edema of the alveolar walls and tortuosity of the alveolar capillaries found in this case, however minimal, may have to some extent impaired oxygen diffusion across the alveolar membrane.

Complete absence of murmurs and murmurs which change from time to time have been reported in proved cases of patent ductus arteriosus. Keys and Shapiro [2] state that atypical and inconstant murmurs are particularly likely to occur in the final stages of failure. Presumably, with sufficient rise in pulmonary blood pressures, the left to right shunt may become diminished or abolished, thus producing changes in or even disappearance of murmurs.

The findings of healed pulmonic endocarditis and acute glomerulonephritis were considered incidental in this case. They in no way contributed to the course which the case took beyond serving as additional reasons for the development of systolic murmurs on the one hand and urinary findings of albumin, casts and red cells on the other. The widely differing ages of these lesions renders unlikely any causal relationship between the two and places them merely in the category of coincidental findings.

The immediate cause of death in this patient was probably cardiac failure, as was suggested not only by his clinical course but also by the signs at postmortem examination of severe hemorrhagic central necrosis, marked cor pulmonale, and right ventricular dilatation.

Summary

An unusual case of patent ductus arteriosus is presented which, clinically, showed prolonged cyanosis, an inconsistent pulmonic diastolic murmur, and polycythemia. At postmortem examination a widely patent ductus arteriosus was demonstrated, together with marked right ventricular hypertrophy and sclerosis of the pulmonary arterial tree. The last two postmortem findings were considered to be manifestations of pulmonic hypertension. We are unable to offer an adequate explanation for the cyanosis. However, the evidence at hand is against the direct passage of blood from the venous to the arterial circulation.

BIBLIOGRAPHY

1. Abbott, M. E.: Atlas of congenital cardiac disease, Am. Heart Assoc., 1936, New York.
2. Keys, A., and Shapiro, M. J.: Patency of the ductus arteriosus in adults, Am. Heart Jr., 1943, xxv, 158.
3. Parker, F., Jr., and Weiss, S.: The nature and significance of the structural changes in the lungs in mitral stenosis, Am. Jr. Path., 1936, xii, 573.

4. Eppinger, E. C., Burwell, C. S., and Gross, R. E.: The effects of the patent ductus arteriosus on the circulation, Jr. Clin. Invest., 1941, xx, 127.
5. Brill, I. C., and Krygier, J. J.: Primary pulmonary vascular sclerosis, Arch. Int. Med., 1941, lxviii, 560.
6. Brenner, O.: Pathology of the vessels of the pulmonary circulation, part III, Arch. Int. Med., 1935, lv, 724.
7. Best, C. H., and Taylor, N. B.: The physiological basis of medical practice, Third Ed., 1943, Williams and Wilkins, Baltimore, p. 621.

FATAL AGRANULOCYTOSIS FOLLOWING THE INTRA-PERITONEAL IMPLANTATION OF SULFANILAMIDE CRYSTALS *

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Comparatively few severe toxic reactions have resulted from the local use of sulfonamide drugs, presumably because relatively small amounts are placed in the tissues and because excretion is prompt.[1] It has been demonstrated that with the dosages used in local application there is only temporary appearance of the drug in the blood.[2, 3] The few severe reactions which have been described relate chiefly to the production of hepatic damage. Watson and Spink [4] reported fatal hepatitis in two individuals who had received sulfanilamide by intra-peritoneal implantation, and Jackson and Coller [3] observed nine instances of jaundice in a group of 62 patients to whom sulfanilamide had been given in the same manner. The development of jaundice in these last nine patients cannot be attributed with certainty to the intra-peritoneal administration because additional sulfanilamide had been given orally as well. Recently there have appeared descriptions of cutaneous reactions which followed the topical use of sulfathiazole ointment.[5, 6] The present report describes a different type of toxic reaction, that of acute agranulocytosis which developed in a patient 17 days after five grams of crystalline sulfanilamide had been placed in his peritoneal cavity. Although agranulocytosis is one of the well recognized complications of sulfanilamide therapy,[7-15] its occurrence after the local use of this drug has not previously been described.

Case Report ‡

F. H., a white man 42 years of age, was admitted to the Barnes Hospital on February 29, 1940, with the history of having recently vomited small amounts of blood. He was known to have had a peptic ulcer for nine years. Roentgenologic examination of his gastrointestinal tract showed the presence of a duodenal ulcer and of pyloric obstruction. He was discharged from the hospital with instructions to adhere to an ulcer-diet and to take alkaline powders. During the next year he had no

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† Research Fellow of the American College of Physicians at the time these observations were made; now 1st Lt. MC, AUS. This article was completed before the author entered military service.
‡ We are indebted to Dr. Glover H. Copher for permission to report this case.

symptoms, and roentgen-ray studies demonstrated less gastric retention than had been present in February, 1940. However, during the summer of 1941 the symptoms of ulcer recurred and he experienced several small hematemeses. Fluoroscopic re-examination of his stomach in February, 1942 showed a greater degree of gastric retention than had been noted the previous year. On February 26, 1942, he vomited large amounts of blood and was again admitted to the hospital.

At this time the patient appeared to be a well nourished man who was neither acutely ill nor uncomfortable. His blood pressure on admission was 120 mm. Hg systolic and 90 mm. Hg diastolic; there were no detectable manifestations of shock. The abdomen was not tender and no masses were felt. The remainder of the physical examination was not remarkable.

The Kahn test was negative. No abnormalities were noted on urinalysis. The non-protein nitrogen content of the blood was 25 mg. per hundred c.c. Guaiac tests for occult blood in the stools were strongly positive. Red blood cell counts varied between 3,370,000 and 4,620,000 per cu. mm., and hemoglobin values ranged from 9.5 to 13.5 gm. per 100 c.c. Other hematologic data are recorded in table 1.

TABLE I

Date	WBC	Differential Count						
		Eos.	Bas.	Myel.	Non-segmented Neutrophiles	Segmented Neutrophiles	Lym.	Mono.
1940								
2–29	9,300	0	0	0	10	63	23	4
1942								
2–26	3,850	0	1	0	2	56	34	7
3–26	2,700	0	0	0	26	42	20	8
3–27	4,650	0	0	0	25	52	18	3
3–30	2,550	0	0	0	0	2	96	2
4–1	400	0	0	0	0	6*	94*	0

* Only 35 cells were found in a complete search of two coverslip preparations.

Transfusions were given and treatment was conservative during the first two weeks of this hospitalization period. However, because of gastric retention and continuing gastrointestinal bleeding, a laparotomy was performed on March 13 under nitrous oxide and ether anesthesia. Scar tissue was found to have completely encircled the first part of the duodenum, where an ulcer had perforated posteriorly into the pancreas. A partial gastrectomy, gastro-enterostomy and jejunojejunostomy were done. Because of presumed contamination of the peritoneal cavity, approximately five grams of sulfanilamide crystals were scattered along the suture lines and over the areas of resection.

Food was well tolerated after 72 hours. The patient's course was uneventful until the evening of his twelfth post-operative day when his temperature rose suddenly to 39.5° C. A fine erythematous rash was noted on his trunk. On the next day he was seen by a dermatologist, Dr. C. W. Lane, who wrote the following note: "The patient has a bright red color of the face, ears, and neck with slight edema of the ears. There is a punctiform erythema of the chest, abdomen and back and a morbilliform rash on the arms, forearms, legs and thighs. No pruritus or burning. No strawberry tongue and no pharyngitis. The color fades readily on pressure. . . ." Dr. Lane considered the skin lesion to be a drug rash and suggested that it had been caused by the sulfanilamide. No sulfanilamide could be detected chemically in blood samples taken on March 28 and March 30. The rash, however, became more intense;

by March 30 the entire skin surface showed a bright erythema, a few small red macular areas were noted on the buccal mucosa, the conjunctivae were intensely injected and severe photophobia was present.

On March 26 the white blood cell count was 2,700 per cu. mm.; there was a marked increase of non-segmented forms of neutrophilic leukocytes. Four days later the granulocytes had almost disappeared; they remained markedly decreased until the patient's death on April 1. The reticulocyte count on April 1 was only 0.2 per cent; the platelet count was 657,000 per cu. mm. Sternal bone marrow obtained by aspiration on April 1 was found to contain very few myeloid cells, a diminished number of nucleated red cells, apparently normal megakaryocytes, and an increased number of small lymphocytes and phagocytic clasmatocytes. The patient was given two additional transfusions. However, on April 1, 19 days after his operation, he developed evidences of bronchopneumonia and died the same evening.

During the 33 days of his final hospitalization period, this man had received, in addition to the sulfanilamide placed in his peritoneal cavity, the following drugs: nembutal .09 gm. at bed-time for five nights, February 26 to March 2; alkaline powders * 1 gm. t.i.d. for 8 days, March 5 to March 13; phenobarbital .03 gm. t.i.d. for 8 days, March 5 to March 13; and morphine sulfate .015 gm. hypodermically four times during the first two days after the operation.

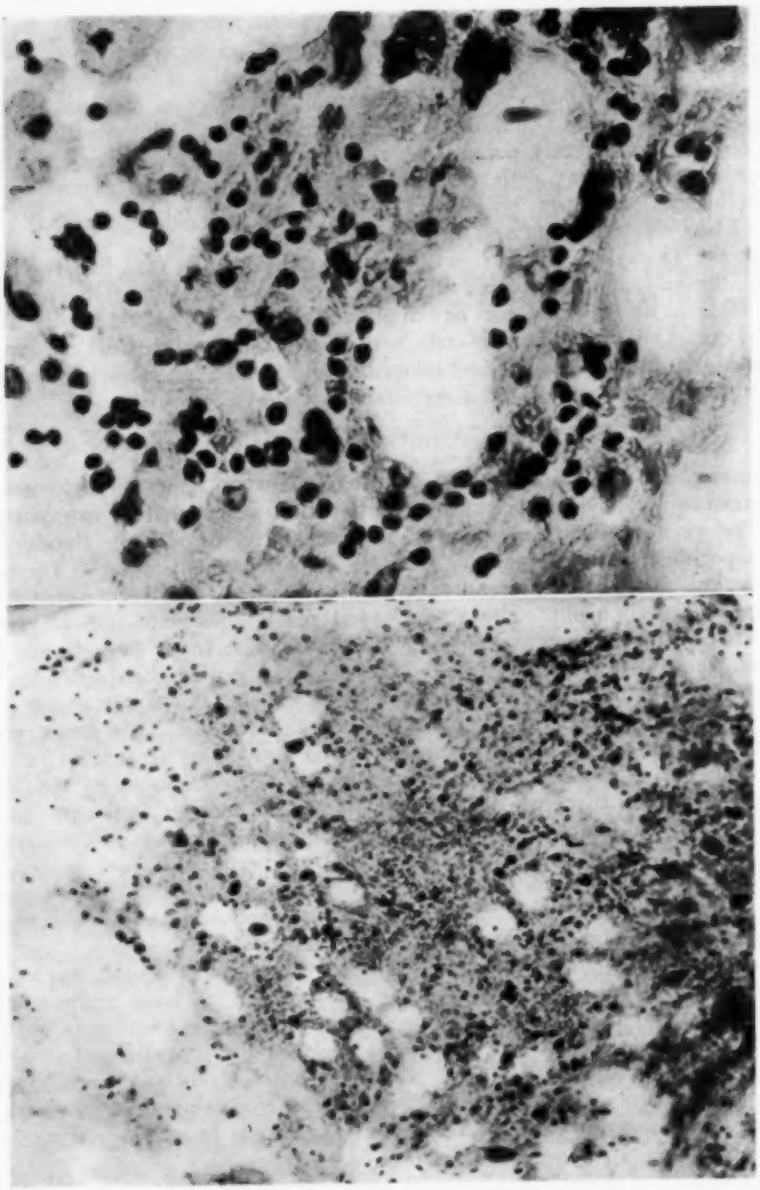
Autopsy Report

The autopsy was performed by Dr. Jane Erganian two hours post mortem. No abnormalities not recorded in the physical examination were noted on external examination. The peritoneal cavity contained about 800 c.c. of slightly cloudy yellow fluid. The peritoneum was hyperemic but was smooth and glistening. There were fibrous adhesions between the omentum, mesentery, and visceral peritoneum and the anterior parietal peritoneum. The wound of a partial gastrectomy with an anastomosis between the jejunum and stomach, and the two limbs of the jejunum at the gastrojejunostomy were partially healed. The proximal end of the duodenum was a blind pouch where it had been severed from the stomach (Polya operation). Each pleural cavity contained 200 c.c. of slightly cloudy yellow fluid. The lungs, particularly the lower lobes, were firm and red in color and a moderate amount of yellowish-red fluid could be expressed from the cut surfaces. The surfaces of the kidneys were slightly granular; there were small petechiae in the mucosa of the pelves. The bone of the sternum and vertebrae was well calcified and there were numerous trabeculae. The bone marrow was yellow and translucent with foci of red, more cellular tissue. The heart, liver, spleen, pancreas, adrenals, urinary bladder, prostate, reproductive organs, and lymph nodes showed no significant gross abnormalities beyond those listed in the final pathologic diagnoses tabulated below.

Sections were taken for microscopic study from the sternal, costal, and vertebral bone marrow, and from all of the viscera. All sections of bone marrow showed marked hypoplasia of the myeloid elements, congestion, and hemorrhage (figure 1). The normal hemopoietic structure was partly replaced by fat cells and there were large areas of mucinous degeneration. Numerous normoblasts and megakaryocytes, both normal and necrotic, were present. Very few myelocytes and no mature granular leukocytes were noted in the sections. A few large cells resembling reticulum cells were observed.

The pulmonary alveoli were filled with large clumps of bacteria, red blood cells, fibrin, and occasional mononuclear cells. No polymorphonuclear leukocytes were present. There were necrosis and slight hemorrhage about the central veins of the liver. Numerous large phagocytic cells were present but no polymorphonuclear cells.

*Composed of calcium carbonate 40 parts, sodium bicarbonate 30 parts, bismuth subcarbonate 20 parts, magnesium oxide 10 parts.



(*a*) × 135 (*b*) × 570

FIG. 1. Bone marrow from vertebra.

The sinusoids of the spleen were greatly dilated and the lining cells protruded into the lumen. Few cells were present in the pulp with only occasional large macrophages and numerous red blood cells. The Malpighian bodies were inconspicuous. Sections of the kidneys showed slight thickening of the basement membranes and of the capsules of the glomeruli. No other pathological lesions were noted in the kidneys. Sections from the heart, pancreas, adrenals, from the wound of the gastroenterostomy, and the inverted stump of the duodenum showed no significant pathological changes.

The final pathological diagnoses were: hypoplasia of the myeloid elements of the bone marrow; central necrosis of the liver; ascites (800 c.c.); petechiae of the mucosa of the sclerae and renal pelves; bronchopneumonia of all lobes of the lungs; hydrothorax (200 c.c.); hydropericardium (100 c.c.); lipoidosis of the pulmonary, coronary, and splenic arteries; arteriosclerosis of the aorta, slight; sclerosis of the anterior leaflet of the mitral valve; arteriolar nephrosclerosis, slight; fenestrations of the cusps of the aortic valve; hemangiomas of the liver; focal hyperplasia of the renal tubules.

Discussion

Acute agranulocytosis developed in this man 17 days after five grams of sulfanilamide had been placed in his peritoneal cavity, and death occurred two days later. Changes in his peripheral blood were characteristic of acute agranulocytosis: profound leukopenia with a selective decrease in granulocytes, a normal platelet count, and no disturbance in red cells. His anemia was apparently caused by gastrointestinal bleeding and did not increase in severity after the operation. Myeloid hypoplasia of the type seen in his bone marrow has frequently been observed in cases of agranulocytosis caused by drug sensitivity or intoxication.

Of the other drugs the patient received, phenobarbital or nembutal might be thought capable of producing agranulocytosis. However, in 1934 the Council of Pharmacy and Chemistry of the American Medical Association, reviewed the published reports which suggested that barbiturates might cause agranulocytosis and concluded that "no definite case has been reported in which a barbiturate alone is responsible."[16] Hadler[17] and others have since reported patients in whom barbituric acid derivatives seemed to have caused granulocytopenia, but in none of these had phenobarbital or nembutal been responsible. It seems unlikely, therefore, that the barbiturate administration had an etiologic relationship to the agranulocytosis in the present case.

Although moderate degrees of leukopenia are frequently produced by therapy with sulfanilamide or its derivatives, agranulocytosis is a relatively rare complication. It rarely develops before the tenth to the fourteenth day after therapy is started.[10] Long and his associates[7] observed that it appeared most frequently between the seventeenth and twenty-fifth days, but might appear as late as the fortieth day of therapy. By this time, large amounts of the drug have usually been given. However, an occasional case has been reported in which relatively small total doses of the sulfonamides have produced agranulocytosis.[11, 13] The interval between initiation of therapy and the development of leukocytic depression has always been 14 days or more even though the duration of therapy and the total amount of drug administered have varied widely. This fact has suggested to a number of observers[14, 15, 21] that the time interval of 14 or more days is the time required for the development of a sensitivity to

the offending sulfonamide drug. It has been suggested that an individual who receives one of the sulfonamide substances a second time might develop agranulocytosis within a few days because of sensitivity produced during previous administration, but this occurrence has not as yet been reported. According to this concept, agranulocytosis produced by sulfonamide drugs is caused by a sensitivity to the chemotherapeutic agent analogous to amidopyrine sensitivity. It is interesting to note that the topical application of sulfathiazole has been observed to induce sensitivity characterized by fever and dermatitis.[18, 20] As far as could be ascertained, this patient had never received sulfanilamide prior to the implantation of five grams in his peritoneal cavity. It is difficult to believe that a dose so small could exert a direct toxic effect on the bone marrow sufficient to cause myeloid hypoplasia and agranulocytosis. The time interval of 17 days is sufficient to have allowed a sensitivity to develop. As far as the authors are aware, this is the first recorded instance in which agranulocytosis has been observed to follow the local or topical application of one of the sulfonamide drugs.

Summary

Description is given of a patient who developed acute agranulocytosis 17 days after five grams of crystalline sulfanilamide had been placed in his peritoneal cavity. Death occurred two days later. He had received no additional sulfanilamide and had not been exposed to other known leukotoxins.

BIBLIOGRAPHY

1. Editorial: Intraperitoneal administration of sulfanilamide, Jr. Am. Med. Assoc., 1942, cxix, 796–797.
2. Mueller, R. S., and Thompson, J. E.: The local use of sulfanilamide in the treatment of peritoneal infections, Jr. Am. Med. Assoc., 1942, cxviii, 189–193.
3. Jackson, H. C., and Coller, F. A.: The use of sulfanilamide in the peritoneum, Jr. Am. Med. Assoc., 1942, cxviii, 194–199.
4. Watson, C. J., and Spink, W. W.: Effect of sulfanilamide and sulfapyridine on hemoglobin metabolism, Arch. Int. Med., 1940, lxv, 825–846.
5. Sams, W. M., and Caplan, L.: Topical treatment with sulfathiazole, Arch. Dermat. and Syph., 1941, xliv, 226–230.
6. Miller, J. L.: Use of sulfanilamide and its derivatives in ointment form: local treatment of cutaneous diseases, Arch. Dermat. and Syph., 1942, xlvi, 379–385.
7. Long, P. H., and Bliss, E. A.: Clinical and experimental use of sulfanilamide, sulfapyridine and allied compounds, 1939, The MacMillan Co., New York.
8. Long, P. H., Haviland, J. W., Edwards, L. B., and Bliss, E. A.: The toxic manifestations of sulfanilamide and its derivatives, Jr. Am. Med. Assoc., 1940, cxv, 364–368.
9. Spink, W. W.: Sulfanilamide and related compounds in general practice, 1941, The Year Book Publishers, Chicago, Ill.
10. Keefer, C. S.: Sulfonamide: its mode of action and its use in treatment of various infections, New England Jr. Med., 1938, ccxix, 562–571.
11. Spain, A. W.: Agranulocytosis following chemotherapy with small dosage, Brit. Med. Jr., 1940, i, 930.
12. Rinkoff, S. S., and Spring, M.: Toxic depression of the myeloid elements following therapy with the sulfonamides: report of 8 cases, Ann. Int. Med., 1941, xv, 89–107.
13. Goldman, L. M., Applebaum, I., and Antopol, W.: Malignant neutropenia following the use of sulfapyridine, Am. Jr. Clin. Path., 1941, xi, 810–817.

14. Shecket, N. A., and Price, A. E.: Fatal granulocytopenia following administration of sulfanilamide, Jr. Am. Med. Assoc., 1939, cxii, 823–828.
15. Pearson, H. E. S.: Fatal agranulocytosis after sulfanilamide therapy, Brit. Med. Jr., 1939, i, 1031–1032.
16. Report of Council on Pharmacy and Chemistry: Relation of amidopyrine and barbituric acid derivatives to granulocytopenia, Jr. Am. Med. Assoc., 1934, cii, 2183–2184.
17. Hadler, A. J.: Granulocytopenia following barbiturate therapy, New England Jr. Med., 1940, ccxxii, 255–259.
18. Livingood, C. S., and Pillsbury, O. M.: Sulfathiazole in eczematous pyoderma: sensitivity reaction to successive local and oral therapy, Jr. Am. Med. Assoc., 1943, cxxi, 406–408.
19. Cohen, M. H., Thomas, H. B., and Kalisch, M. D.: Hypersensitivity produced by the topical application of sulfathiazole, Jr. Am. Med. Assoc., 1943, cxxi, 408–411.
20. Weiner, A. L.: Cutaneous hypersensitivity to topical application of sulfathiazole, Jr. Am. Med. Assoc., 1943, cxxi, 411–413.

HYPERPARATHYROIDISM, WITH FAILURE TO RECALCIFY AFTER REMOVAL OF PARATHYROID ADENOMA (A CASE REPORT) *

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Hyperparathyroidism due to adenoma is usually followed by recalcification after removal of the tumor. The present report cites a case which was unusual in its failure to deposit calcium in the bones during a five year period after removal of the tumor, despite lack of evidence of a recurrence of hyperparathyroidism. The preoperative and immediate postoperative course of this patient was reported by Gutman and Parsons,[1] and it will only briefly be outlined here.

Case Report

The patient, M. B., was a 54 year old Syrian spinster who was admitted to the Presbyterian Hospital in June 1937 with a 13 year history of repeated pathological fractures, with non-union, and subsequent skeletal deformities. There was no history of renal colic, polydipsia or polyuria. Roentgenography one and one-half years before admission (January 10, 1936) showed generalized skeletal decalcification in addition to cystic and fibrotic changes.

Examination on admission (June 14, 1937) showed marked skeletal deformities. The legs were atrophied, shapeless and bizarrely contorted. The pelvis was tilted to left. A rounded dorsal kyphosis was present. The skull was enlarged; the chin rested on the sternum because of shortening of the neck. Pronounced prognathism was present. There were obvious bony deformities of both arms. The bones of the legs were extremely tender to pressure, and there was some tenderness over the ribs, spine and arms. A nodular mass was palpable in the left side of the neck.

Laboratory data revealed: (1) Hypercalcemia (12.6 to 13.7 mg. per cent), hypophosphatemia (1.8 to 2.1 mg. per cent), and a consistently normal serum phosphatase

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level (2.7 to 3.0 Bodansky units). (2) Skeletal roentgenograms showing generalized decalcification of an extreme degree, especially of the lower legs, in which there were numerous cysts and in addition, cysts in the deformed and decalcified pelvis and in the ribs, which like the other bones were the seat of numerous fractures. (3) Normal blood count. (4) Normal urine except for a rare red blood cell. (5) Phenolsulfonphthalein excretion (intramuscular) of 37 per cent in two hours. (6) Calcium balance studies on a low calcium intake showing that the excretion of calcium in the urine (which is usually high in this condition) was not excessive.

Exploration in July 1937 revealed a tumor 2.0 by 1.2 by 0.5 cm. inferior to the left pole of the thyroid gland. The remaining parathyroid tissue was identified and no other parathyroid tumor was found. Histologically the mass removed was found to be a parathyroid adenoma. It was composed of chief cells, some of which were transitional to the water-clear type, and many rose-red cells.

Twenty-four hours after the removal of the tumor the serum calcium had fallen to 10.4 mg. per cent. The value a week previously had been 12.8 mg. per cent. The

TABLE I

Preoperative and Postoperative Serum Calcium, Phosphorus and Phosphatase Values

Date	Ca. mg. %	P. mg. %	Phosphatase (Bodansky units)
7- 6-36	13.7	1.8	2.9
6-17-37	12.6	2.1	3.0
7- 2-37	12.8	1.9	2.7
7- 9-37	Parathyroid Tumor Removed		
7-10-37	10.4	2.4	2.7
7-12-37	9.0	2.8	2.2
7-14-37	10.3	2.4	3.1
7-19-37	9.5	2.7	3.3
7-13-38	10.0	2.9	2.5
2-28-39	10.1	3.6	2.9
8-22-39	9.5	3.1	3.0
4- 6-40	11.0	2.7	1.5
3- 5-41	10.5	2.7	2.6
9- 5-41	10.1	2.9	4.0
10-12-41	10.9	3.9	3.6
5- 4-42	9.4	3.7	2.4

patient was given 15 grams of calcium lactate a day for the six weeks following operation. A month postoperatively, roentgenogram revealed an elongated shadow of increased density in the region of the orifice of the left ureter. No such shadow was noted in roentgenograms taken a month before operation. This same shadow was still present in a roentgenogram of the kidney-ureter-bladder tract taken in December 1939. There had been no history of renal colic; urinalysis still showed a rare red blood cell. Phenolsulfonphthalein excretion (intramuscular) was 32 per cent in two hours in December 1942 as compared with 37 per cent in two hours before operation.

In 1942 the patient's status was very similar to that found immediately after operation. There had been no change in serum phosphatase activity, the values ranging from 1.5 to 4 Bodansky units; serum calcium values varied from 9.0 to 11.0 mg. per cent; serum phosphorus values lay between 2.4 and 3.9 mg. per cent. In July, 1941 the patient fractured the right tibia. The fracture healed by fibrous union but with no evidence of recalcification. Comparison of roentgenograms taken in November, 1941 with those of January, 1936 show an unchanged cystic and decalcified appearance of the bones despite the maintenance of normal serum calcium values (figures 1 and 2).

There has been no evidence of recurrence of hyperparathyroidism as seen from (1) normal serum calcium and phosphorus values, (2) calcium balance studies in August, 1939 showing that there has been no excessive urinary calcium excretion on a low calcium intake, (3) bone biopsy in August, 1939 showing an absence of osteoclasts and osteoblasts and suggesting that a long-standing condition had reached an equilibrium, (4) roentgenographic studies of the bones in November, 1941 showing no further decalcification.

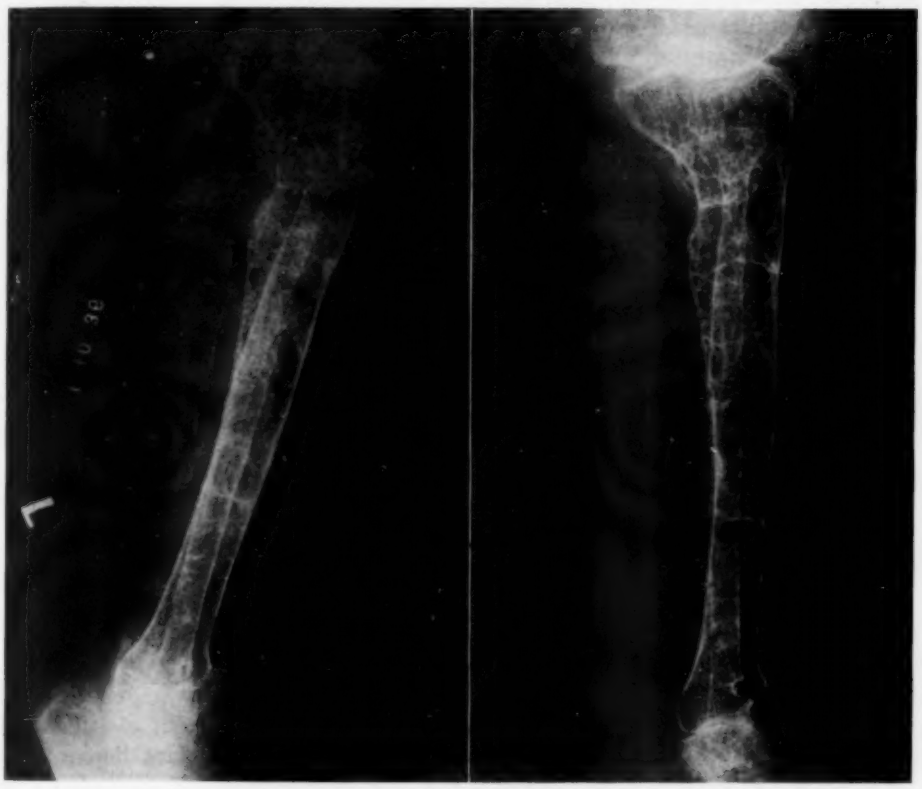

FIG. 1. (*Left*) Roentgenogram of the left leg taken one and one-half years before operative removal of parathyroid adenoma.
FIG. 2. (*Right*) Roentgenogram of same leg four years after removal of parathyroid adenoma showing no changes in the cystic and decalcified appearance of the bones.

DISCUSSION

Failure of recalcification in hyperparathyroidism due to adenoma after removal of the tumor might conceivably be related to two factors: the diminution of osteoblastic activity resulting in the lack of newly formed osteoid tissue; or, the absence of available calcium for deposit in the tissue.

This latter consideration seems unlikely because of adequate to excessive calcium intake, persistent normal serum calcium values and questionable renal calculus formation, the latter suggesting that adequate calcium was absorbed and available for deposition. Consequently, diminution in osteoblastic activity would

appear to offer the better explanation. A measure of this activity is reflected in the serum phosphatase level. In contrast to most cases of hyperparathyroidism with bone changes, the serum phosphatase level in this instance was not elevated previous to operation nor was it changed in the five subsequent years. As was suggested in the original paper by Gutman and Parsons, it is possible that when bone destruction is so extreme and of such long standing, osteoblastic activity comes to a standstill. The findings in this case lend weight to this hypothesis. It might, therefore be anticipated that in the absence of increased osteoblastic activity or of increased serum phosphatase levels, recalcification would not occur.

SUMMARY

(1) A case of hyperparathyroidism due to adenoma is presented. There was failure of recalcification five years following the removal of the tumor despite lack of evidence of recurrence of hyperparathyroidism.

(2) The failure of the bones to recalcify despite the prolonged normal serum calcium level is attributed to the lack of increased osteoblastic activity. Arrested osteoblastic activity is suggested by the normal preoperative and postoperative serum phosphatase levels.

BIBLIOGRAPHY

1. GUTMAN, A. B., and PARSONS, W. B.: Hyperparathyroidism simulating or associated with Paget's disease; with three illustrative cases, ANN. INT. MED., 1938, xii, 13–31.

UNCONTROLLABLE HEMORRHAGE AFTER DICOUMAROL THERAPY WITH AUTOPSY FINDINGS *

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INTEREST in anti-coagulants as therapeutic agents has encouraged the trial of various substances in conditions characterized by intravascular clotting with resultant thrombosis and embolism. During the past few years heparin has occupied a leading rôle in this respect, until the discovery of the part played by spoiled sweet clover in the production of hemorrhagic disease of cattle.[1] The recognition of the active principal, dicoumarin (3,3′ Methylenebis [4-Hydroxy-coumarin]), its isolation and synthesis by Link and his coworkers,[2] have paved the way for its therapeutic employment in man.

Most reports thus far in the literature have described the beneficial results from its use, whereas others have also mentioned certain untoward effects attributed to it.[3] Its mode of action is as yet only slightly understood, its toxicity is but little known, and its usefulness, particularly as compared with heparin, questionable. In animals observed experimentally, toxicity is manifested by hemorrhages in muscles, aponeuroses, the gastrointestinal tract, pleural spaces and lungs. Marked dilatations of the capillaries, small arteries and veins have been noted, but no parenchymatous changes found.[4] In man, evidence of hemor-

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rhages in the urinary tract and intestines has been observed.[11] However, the following case with postmortem findings illustrates that severe hemorrhages contributing to death may attend the administration of dicoumarol.†

Case Report

K. O., female, 79 years of age, was admitted to the Jewish Hospital of Brooklyn on December 9, 1942, with hematuria of three days' duration and bleeding from the gums for five days. Four weeks before admission she complained of visual difficulty in her right eye. She was admitted to another hospital, where a diagnosis of "thrombosis of the right retinal vein" was made, following which, 100 mg. of dicoumarol were administered orally each day for 21 days. During this time no prothrombin estimations were made, although the coagulation time was found to be about 20 minutes. Four days before admission to the Jewish Hospital, bleeding from the gums was noted, and dicoumarol was discontinued. Two days later hematuria set in, which persisted up to the time of admission.

Table I

Date	C.T.	P.T.	C.	Remarks
Dec. 9	39′30″			Transfusion, oozing ceased
10	20′45″	60.6″	12.1″	Transfusion, oozing ceased
11	11′35″			
12	9′25″			Transfusion, oozing ceased
14	9′15″	96.8″	13.9″	
15				Oozing cardiac condition poor
16	49′+	360+″	13″	Transfusion
17	20′	83.1″	11.2″	Ecchymoses, comatose, transfusion
18	11′20″	84.4″	12.8″	Transfusion
19				General ecchymoses, transfusion
21	28′30″			

C.T., Coagulation time (capillary tube method); P.T., Prothrombin time (Sherber method); C., Control.

Her past history disclosed a long standing hypertension and a "chronic anemia" for which 0.5 c.c. of reticulogen had been given every six weeks. She had had a gall-bladder operation many years before; no calculi were found and an appendectomy was performed.

Physical Examination: The patient was a coöperative and rational elderly female with normal temperature, pulse and respirations. The blood pressure was 200 mm. Hg systolic and 100 mm. diastolic. The pertinent physical findings were partial bilateral deafness, and regular, round, equal pupils which reacted to light and accommodation. Vision of the right eye was blurred. "In the region of the inferior temporal retinal vein on the right side, there was a large purplish hemorrhagic area extending out toward the macular region; there was moderate tortuosity of the vessels and slight arteriovenous inclining of both fundi; there was no exudate and the discs appeared normal." There was a slight bloody ooze from the gums. The heart was somewhat enlarged to the left, the sounds were distant and a soft systolic murmur was heard over the entire precordium. Over the extremities ecchymoses of different sizes were seen. The spleen and liver were not palpable. The clinical diagnosis was "generalized arteriosclerosis, hypertensive and arteriosclerotic cardiovascular disease, thrombosis of the right inferior temporal vein and bleeding secondary to dicoumarol ingestion."

The course in the hospital was a very eventful one. She was given a transfusion

† Dicoumarol is the trademark for the commercial preparation of Dicoumarin.

of 300 c.c. of fresh citrated blood on the day of admission. Following its administration, oozing from the gums ceased and the next morning there was no blood in the urine. However, on the following day, bleeding from the gums recurred, and she was given transfusions of 250 c.c. of citrated blood on the second and third days respectively. Bleeding ceased after these transfusions only to recur within the next 12 hours. During her stay she received a total of seven transfusions (table 1). Following the second, she developed acute left heart failure with marked cardiac irregularity due to premature auricular contractions. In the attempt to avoid myocardial embarrassment, subsequent transfusions were preceded by venesections. After the fourth hospital day she became dyspneic, orthopneic and cyanotic. Repeated phlebotomies were performed and she was given aminophyllin with transient relief. She then developed auricular fibrillation, digitalization was begun and she was placed in an oxygen tent. On the seventh day she had urinary retention for 24 hours. The following day progressive drowsiness set in, and she became unresponsive and incontinent. She grew progressively worse, lapsing into coma, and died on the fourteenth hospital day. The temperature ran an irregular course between 99° and 103° F., pulse rate between 70 and 100 per minute and the blood pressure gradually declined to 110 mm. of Hg systolic and 70 mm. diastolic.

Autopsy Findings

Gross: The body was that of a well developed and well nourished elderly female 155 cm. in length and weighing 53 kg. There were varying sized ecchymotic areas on both shoulders, anus, hips and legs. The lips were pale. Most of the teeth were still present and were in fair condition. There was dried blood on the gums. The buccal mucosa was pale. In the retroperitoneal tissues of the left lower quadrant there was a large suffusion of blood.

The heart weighed 440 gm. The mitral valve cusps were slightly thickened. The aortic valve leaflets were thickened and there were calcified knobs on the free edges. There was no separation of the commissures. The ascending aorta was dilated to a circumference of 10.3 cm., at its widest portion. Within the wall of the entire aorta there were numerous, stony hard plaques. The coronary arteries were tortuous and their walls contained many calcified plaques which in places projected into the lumen. The trachea and bronchi contained a moderate amount of pink, frothy fluid. The lungs were buoyant and crepitant. On section the cut surfaces were pink-gray with areas of red especially in the lower lobes. Pink frothy fluid could be expressed from the surface on pressure.

The liver measured 29 by 12 by 7 cm. and weighed 1,100 gm. The external surface was brown, smooth and glistening. On section the color was deep mahogany. The markings were unusually distinct, pin head sized, deeper brown areas being separated from one another by slightly depressed grayish strands.

The spleen measured 12 by 8 by 2 cm. and weighed 90 gm. The capsule was slate blue in color. On section the fibrous markings were prominent.

The pancreas measured 17 by 6 by 4 cm. and weighed 80 gm. It was pink-gray in color, and the lobulations were distinct. The splenic artery was sclerotic and ran a tortuous course along the superior surface of the organ. Its wall contained many firm plaques.

The right kidney weighed 110 gm., the left 140 gm. The capsules stripped easily revealing a coarsely granular brown surface. On section, the markings were distinct. There were several irregularly shaped hemorrhagic areas in both pelves, more extensive in the left than in the right. Within the bladder wall there were many hemorrhages near the trigone. On section these appeared to be situated just beneath the mucosa (figure 1).

The marrow in the ribs and vertebrae was red-brown in color, and semi-fluid in consistency. In the right tibia the myeloid cavity was filled with bright yellow adipose tissue.

The cranial bones were unusually thick; the calvarium in the frontal region measured 1 cm. in thickness. The dura mater stripped from the bone fairly easily and was discolored red-brown. The vascular sinuses were not unusual, although the veins in the dura were prominent and dilated. In the subdural space, attached to the dura and covering the cerebral hemispheres was a layer of soft, jelly-like, red-blue, clotted blood, most of which could be reflected with the dura (figure 2). In the base

FIG. 1. Subdural hemorrhage, dura mater partially reflected.

of the skull, in the subdural space, especially in the middle fossae, similar extravasations were seen (figure 3). No lacerations of the meninges or fractures of the bones of the skull could be found; nor could any obvious source of the hemorrhage be demonstrated.

The brain weighed 1,220 gm. Loosely attached to the pia arachnoid over the right cerebrum was a membranous layer of gray fibrinous material. The pia arachnoid was delicate; the veins were widely dilated. There were collections of blood within the subarachnoid space. The gyri were narrower and the sulci broader than usual. The arteries at the base of the brain were elongated, tortuous, and their walls were almost stony hard in places. The left posterior cerebral artery was 1½ times as large

as the right. On section, the hemorrhage was seen to be restricted to the subarachnoid space, and no extravasations could be seen in the brain or ventricles.

Microscopic: Heart and Aorta: The blood vessels of the epicardium were greatly dilated and engorged. The myocardial cells were arranged in bundles separated by thin or moderately thick fibrous tissue trabeculae. The cells showed no unusual features, except in many places where delicate or coarse bundles of fibrous tissue lay between them. Here the myofibrils were swollen or shrunken, greatly distended, with granular pale staining cytoplasm and various sized nuclei. The coronary arteries showed a mild degree of sclerosis. The intima of the aorta was broad and wavy in

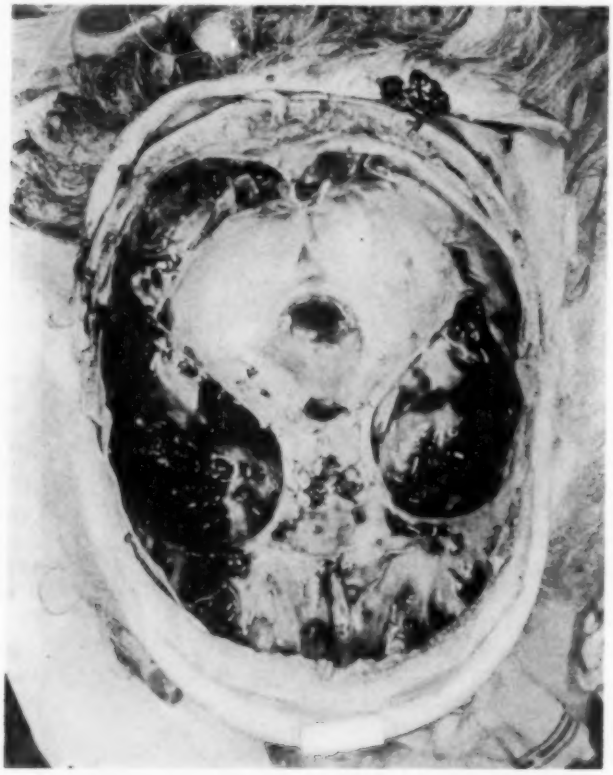

FIG. 2. Hemorrhage in base of skull.

outline, consisting chiefly of parallel lamellae of homogeneous pink staining material, separated in places by irregular plaques of lighter pink staining amorphous substance or clear boat-shaped clefts. Occasionally large collections of this pale staining material were seen, and in these the clefts were numerous. Masses of granular purple staining substance were also seen. In the media the muscle fibers and elastic fibers were separated in places by small variable sized irregular patches of violet staining amorphous material, and in others by elliptical shaped clefts. The adventitia was broad, being composed of adipose and fibrous tissue. A few small areas of perivascular round cell infiltration were seen.

Lungs: The alveoli varied much in size, most were larger than usual, and in some the septa were interrupted or missing. Many small patches of alveoli contained a pink staining, homogeneous, amorphous material, a few large mononuclear cells,

and some degenerated leukocytes. Occasionally there was an area in which the alveoli were slit-like and appeared to be compressed. In other places the parenchyma was replaced by large patches of fibrous tissue containing particles of black pigment and thickened blood vessels. The interalveolar septa throughout were prominent, the capillaries being greatly dilated and filled with blood. They thus presented a striking picture, especially in the edematous areas, where they stood out prominently in contrast to the pale staining coagulated edema fluid. The larger blood vessels, both arteries and veins, also were dilated and engorged. The bronchi in some places were collapsed, with narrow lumina, and stellate arrangement of the mucosa. In these the lumina were dilated and contained an amorphous granular material, leuko-

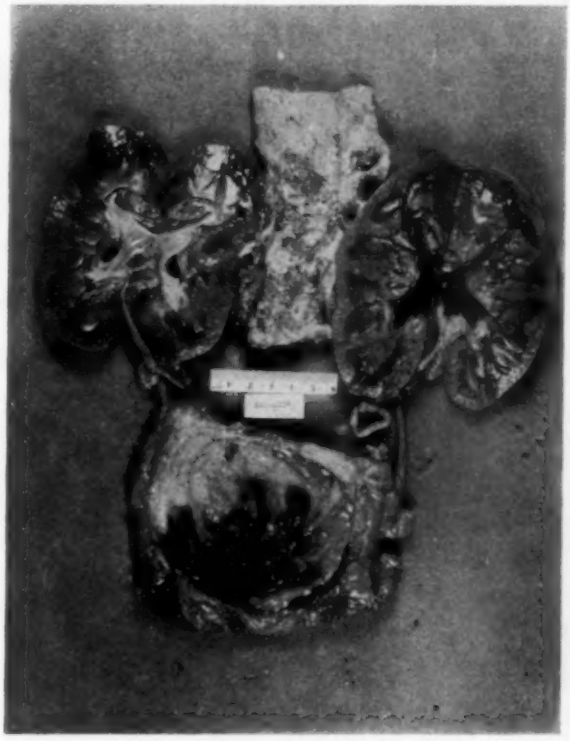

FIG. 3. Hemorrhage in pelves of kidneys and in urinary bladder.

cytes and much desquamated epithelium; the muscularis in these appeared thickened. In the submucosa there was a mild infiltration of polymorphonuclear neutrophilic leukocytes, small round and plasma cells. The medium sized and small arteries and veins, as well as the arterioles and venules were greatly dilated, and in most instances engorged with blood.

Liver: Glisson's capsule was composed of a broad layer of closely packed fibers which contained a few pale staining nuclei and assumed a wavy appearance. In the subcapsular regions there was a scattering of small and large round cells. The architectural pattern of the liver was distorted and disarranged. The lobules varied greatly in size, and were spherical, polygonal or irregular in shape. Many were surrounded by narrow or broad bands of fibrous tissue, composed of coarse or delicate strands, containing occasional oval, or spindle shaped, deeply staining vesicular nuclei.

In many there were focal or diffuse collections of small round cells and a few plasma cells. The normal relationship between portal areas, central veins and hepatic lobules was altered. In many of the lobules the liver cells were arranged in a crude cord-like fashion, many pseudo-cords anastomosing in a haphazard and irregular fashion. The usual radiating appearance was missing. The hepatic cells varied considerably in size; some were cuboidal, whereas others showed only a slight cuboidal or polyhedral shape. The nuclei varied a bit in size; all were spherical. The cytoplasm of most cells was coarsely granular; in others it contained vacuoles. In most of the latter the nuclei were situated at the periphery of the lobule in large groups, but a few smaller ones were seen in the central portion. With the Scharlach R stain on frozen sections, the contents of these vacuoles stained bright red. In a few scattered areas the cells were greatly swollen, the cell membranes were indistinct, the

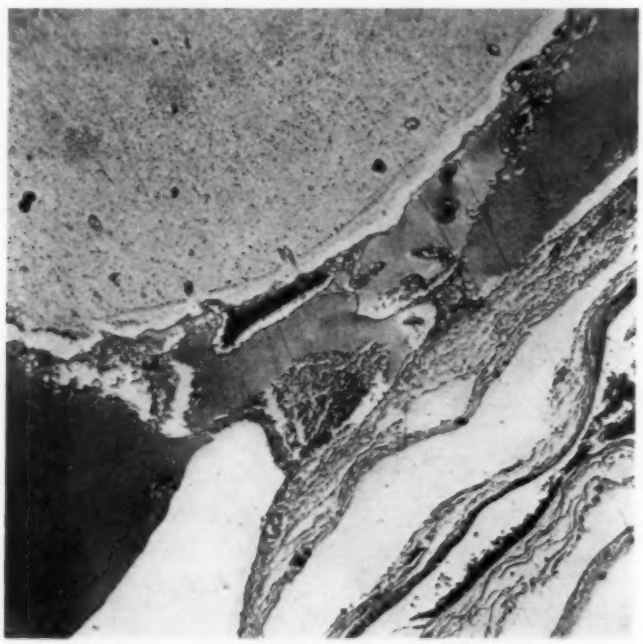

FIG. 4. Hemorrhage in pia-arachnoid: dilatation of blood vessels.

cytoplasm was pale staining, finely granular and contained numerous small vacuoles. These areas were fairly well circumscribed. The Kupffer cells were fairly prominent. The sinuses were very wide and were filled with erythrocytes and a few leukocytes. In many of the portal areas there was a variable increase in fibrinous tissue and in some there were collections of small round cells. The portal veins and hepatic arteries were not increased in size or engorged.

Kidneys: The capsules were thickened, and made up of fibers containing a few small round cells. The number and distribution of glomeruli were as usual. A few showed transformation into hyaline amorphous structures, and some were surrounded by small amounts of fibrous tissue and focal infiltrations with small round cells. The tubular epithelium showed only some swelling and granular changes in places. In the pelvis between the muscularis and mucosa there was an extensive diffuse extravasation of blood. The wall of the urinary bladder was markedly thickened; beneath the mucosa was a large infiltration with blood.

Spleen: The capsule was composed of a broad layer of many connective tissue fibers, containing a few oval nuclei. The follicles appeared to be of the usual number, but were rather small, and in none were there germinal centers. The walls of the central arteries were thick; their lumina were narrow. The muscularis for the most part was replaced by broad bands of collagen or amorphous hyalinized material. They were surrounded by irregularly shaped islands of small round cells, the borders of which merged imperceptibly with the adjacent pulp. The latter appeared chiefly as a pattern of very loosely arranged spindle shaped cells, with long, delicate, anastomosing processes. Their nuclei were long, oval, vesicular and when vesicular, bulged into the lumen. The sinuses in most places were extremely large and dilated, containing many erythrocytes, some polymorphonuclear neutrophilic leukocytes, small and large round cells and a few immature myeloid elements. In some areas, there were large collections of blood, in which no splenic elements could be recognized.

Lymph Node: The capsule was thin; the follicles were ill-defined and in them the cells were scattered diffusely. They consisted chiefly of small and round cells and some polynuclear eosinophiles. The organ appeared to be the seat of a diffuse edema.

Bone Marrow: The vertebrae and ribs showed the usual distribution of hemopoietic and adipose tissue. From the tibia it consisted exclusively of adipose tissue.

Meninges and Brain: Sections taken from the cerebrum and cerebellum showed extensive extravasations of blood in the meshes of the pia-arachnoid, as well as in the subarachnoid and subdural spaces (figure 4). No coagulated material or fibrin could be recognized. The small arteries, veins and capillaries were greatly dilated and engorged with blood. Sections taken from various regions throughout the brain showed no unusual features.

Pituitary Gland: Showed a marked dilatation and engorgement of the capillaries.

Anatomic Diagnosis: Arteriosclerosis, generalized with particular involvement of: (*a*) coronary arteries with myofibrosis cordis; (*b*) aorta with aneurysmal dilatation; (*c*) renal arteries with nephrosclerosis; (*d*) cerebral arteries; hypertrophy and dilatation of heart; cirrhosis of liver; fibrous pleural and peritoneal adhesions; scars of operations; absence of appendix.

Hemorrhages in meninges, skin, retroperitoneal tissues, pelves of kidneys, urinary bladder, stomach and duodenum.

Comment

The main feature of the necropsy findings was the marked engorgement of all the blood vessels, excepting the larger trunks. It was most pronounced in the capillaries, arterioles and venules, and much more prominent than that usually seen post mortem in other conditions. The lumina of the vessels were broad and in all instances contained well preserved blood elements. In the liver and meninges, the impression was that of a relaxation of the vessel walls. Where the hemorrhages had occurred, no solution of continuity of the wall could be recognized. The probability is that such extravasations were due to diapedesis between cells, rather than to rupture or solution of continuity of the cell walls. This would explain the histologic picture and the rather limited foci of hemorrhage, especially where the bleedings were spontaneous and not connected with trauma however slight, as in the meninges and pelves of the kidneys. As a matter of fact, the hemorrhagic lesions resembled those seen in the purpuras, particularly the essential variety. The difference between the two, however, lies in the appearance of the blood vessels and sinuses. In the spleen it was striking in that the sinuses were greatly distended in many places, appearing as

pools of blood, bounded by intact sinus walls, with no obvious blood seepage. In the more extreme stage, frank hemorrhage with disappearance of splenic pattern was also seen. In the liver too, many places were seen with distended sinuses and clearly outlined cellular walls, filled with unchanged, unclotted blood. This is quite in accordance with the lesions produced in dogs by Bingham, Meyer and Pohle, after feeding dicoumarin in varying dosage.[14] No parenchymatous lesions were seen except occasionally some hydropic changes in the liver cells. In all dogs receiving fatal doses, hemorrhages were demonstrated at some site. All had some subcutaneous and intramuscular extravasations, while frequently evidence of hemorrhage was found in the gastrointestinal tract, pleural spaces or lungs. The dilatation of capillaries, small arteries and veins was especially striking in those animals dying acutely from massive doses. This was also observed sometimes to a lesser degree in animals receiving small doses and sacrificed for pathological study.

Whether the mild degree of cirrhosis of the liver contributed to the toxic action of dicoumarin in this case by exaggerating the prothrombin deficiency cannot be decided at this time. Certain observers [11, 16] suggest that dicoumarin interferes in some way with the prothrombin producing function in the liver and conclude that disease of the liver, or interference with its efficiency may be a predisposing factor to the establishment of a pathologic dicoumarin state and to the prolonged coagulation time of the blood. Assuming that this is likely, even though not proved, it cannot be the whole explanation for the hemorrhages. There still remains to be explained the extravasations that were found without any obvious lesions in the blood vessels. Here, the similarity to essential thrombocytopenia strikes one, with its multiple hemorrhages due apparently to some agent disturbing the normal permeability of the vascular system. Lalich, Lalich and Copley [17] suggest, as the result of experiments on mice receiving the hemorrhagic agent, that a deficiency of a hypothetical skin or tissue factor may play a rôle in the mechanism in producing the bleeding state.

The mechanism of blood coagulation is affected by dicoumarin through its action in producing a hypoprothrombinemia, as manifested experimentally and clinically [12] by a prolongation of prothrombin time. In this case, the prothrombin time was greatly increased, varying between 60.4 seconds to over 6 minutes.

The coagulation time was also significantly prolonged, but could be ameliorated temporarily by transfusion, as shown in table 1. This dicoumarin state with its abnormal clotting manifestation persisted for 18 days after the administration of dicoumarin had been discontinued, up to the time of death. Transfusions afforded a temporary means of restoring the normal clotting factors, probably through the instrument of the parenteral introduction of prothrombin. Clinically, this confirms the observations made by Prandoni and Wright,[11] Davidson and MacDonald,[12] and Barker, Allen and Waugh,[16] in regard to the behavior of the prothrombin and coagulation times in response to transfusion. The transitory benefit is sustained until the extraneous supply of prothrombin is exhausted. Bleeding then recurs and the previous dicoumarin state characterized by hypoprothrombinemia is resumed. There is no satisfactory explanation for this state, although clinical and experimental observations suggest that the dicoumarin interferes with prothrombin production at its source, rather than by acting as a neutralizing or inactivating agent of the prothrombin in the

blood stream or tissues. Whatever the mechanism, the prothrombin concentration is reduced to low levels during and persisting for some time after adequate dicoumarol administration.[8] Its continued use must be controlled uninterruptedly by prothrombin estimations. When the level falls to the danger point, the drug must be discontinued at once. If the latter is delayed until actual bleeding prevails, it may become impossible to control, as this case illustrates.

What is the dangerous level of prothrombin? Davidson and MacDonald [12] state that "the administration of dicoumarol should be controlled so that the prothrombin concentration be kept within reasonable limits." "However, to obtain a fairly constant and significantly delayed coagulability of the blood, one must reduce the prothrombin concentration to very low levels, and if this is done, the effect of the drug cannot be adequately controlled. Thus one must sacrifice control for effectiveness or vice versa." On the other hand, Bingham, Meyer and Howard [13] corroborating the experience of Butt, Allen and Bollman [8] and others, aim to maintain the prothrombin time not beyond 19 seconds (25 per cent) and the coagulation time between 15 and 20 minutes. Barker, Allen and Waugh [16] more recently in the study of 497 surgical cases advise sufficient dosage to secure a prothrombin time from 35 to 60 seconds, their normal being 18 to 22 seconds. We do not feel that this question can be answered with finality at present. Until this point is settled, it would appear that dicoumarol is a potent drug and its use still in the experimental stage.

Conclusions

1. A case is presented in which an uncontrollable dicoumarin state was produced.

2. Citrated transfusions were only partially and ineffectually successful in combating this state.

3. Uncontrollable bleeding due to dicoumarin action contributed to the death of this patient.

4. Dicoumarol should not be administered unless daily blood prothrombin and coagulation times can be accurately determined and the patient kept under close observation.

BIBLIOGRAPHY

1. Schofield, F. W.: Damaged sweet clover: The cause of a new disease in cattle simulating hemorrhagic septicemia and blackleg, Jr. Am. Vet. Med. Assoc., 1924, lxiv, 553–575.
2. Campbell, H. A., Roberts, W. L., Smith, W. K., and Link, K. P.: Studies on the hemorrhagic sweet clover disease I, Jr. Biol. Chem., 1940, cxxxvi, 47–55.
3. Campbell, H. A., and Link, K. P.: Studies on the hemorrhagic sweet clover disease IV, Jr. Biol. Chem., 1941, cxxxviii, 21–33.
4. Campbell, H. A., Smith, W. K., Roberts, W. L., and Link, K. P.: Studies on the hemorrhagic sweet clover disease II, Jr. Biol. Chem., 1941, cxxxviii, 1–20.
5. Huebner, C. F., and Link, K. P.: Studies on the hemorrhagic sweet clover disease VI, Jr. Biol. Chem., 1941, cxxxviii, 529–534.
6. Overman, R. S., Stahman, M. A., Sullivan, W. R., Huebner, C. F., Campbell, H. A., and Link, K. P.: Studies on the hemorrhagic sweet clover disease VII, Jr. Biol. Chem., 1942, cxlii, 941–954.
7. Stahman, M. A., Huebner, C. F., and Link, K. P.: Studies on the hemorrhagic sweet clover disease V, Jr. Biol. Chem., 1941, cxxxviii, 513–527.

8. Butt, H. R., Allen, E. V., and Bollman, J. L.: A preparation from spoiled clover which prolongs coagulation and prothrombin time of the blood—preliminary report of experimental and clinical studies, Proc. Staff Meet. Mayo Clin., 1941, xvi, 388–395.
9. LeFevre, F. A.: The effect of 3,3′ Methylene-Bis(4-Hydroxycoumarin) Dicoumarol on the prothrombin and coagulation time of the blood, Cleveland Clin. Quart., 1942, ix, 147–152.
10. Townsend, S. R., and Mills, E. S.: The effect of the synthetic hemorrhagic agent 3,3′ Methylene-bis(4-Hydroxycoumarin) in prolonging the coagulation and prothrombin time in the human subject, Jr. Canad. Med. Assoc., 1942, xlvi, 214–218.
11. Prandoni, A., and Wright, I. S.: The anti-coagulants heparin and the dicoumarin 3,3′ Methylene-Bis(4-Hydroxycoumarin), Bull. New York Acad. Med., 1942, xviii, 433–455.
12. Davidson, C. S., and MacDonald, H.: Critical study of action of 3,3′ Methylenebis (4-Hydroxycoumarin) dicoumarin, Am. Jr. Med. Sci., 1943, ccv, 24–33.
13. Bingham, J. B. Meyer, O. O., and Howard, B.: Studies on the hemorrhagic agent 3,3′ Methylenebis(4-Hydroxycoumarin) III, Am. Jr. Med. Sci., 1943, ccv, 587–594.
14. Bingham, J. B., Meyer, O. O., and Pohle, F. J.: Studies on the hemorrhagic agent 3,3′ Methylenebis (4-Hydroxycoumarin) I, Am. Jr. Med. Sci., 1941, ccii, 563–578.
15. Meyer, O. O., Bingham, J. B., and Axelrod, V. H.: Studies on the hemorrhagic agent 3,3′ Methylenebis (4-Hydroxycoumarin) II, Am. Jr. Med. Sci., 1942, cciv, 11–21.
16. Barker, N. W., Allen, E. V., and Waugh, J. M.: The use of dicoumarol (3,3′ Methylenebis) 4-Hydroxycoumarin in the prevention of postoperative thrombophlebitis and pulmonary embolism, Proc. Staff Meet. Mayo Clin., 1943, xviii, 102–107.
17. Lalich, J. J., Lalich, M. H., and Copley, A. L.: Bleeding time in mice following oral administration of 3,3′ Methylene-bis (4-Hydroxycoumarin), Surgery, 1943, xiii, 316–321.

EDITORIAL

HISTOPLASMOSIS

INFECTION with the yeast-like organism histoplasma was first reported in 1906 by Darling, who discovered three cases of the infection in the course of a systematic search for kala azar in the Canal Zone. Clinically the disease in Darling's [1] cases was "characterized by splenomegaly, emaciation, irregular pyrexia, leukopenia and anemia." The pathologic lesions he described as "the invasion of endothelial cells in the smaller lymph and blood vessels and capillaries by enormous numbers of a small encapsulated organism (*Histoplasma capsulatum*) causing necrosis of the liver with cirrhosis, splenomegaly, pseudogranuloma of the lungs, small and large intestines with ulceration of the latter, and necrosis of the lymph nodes draining the infected viscera." He regarded the organism as a protozoan parasite.

The disease was long regarded as a rare tropical infection, since 20 years elapsed before another case was reported (by Watson and Riley in Minnesota in 1926). Since 1934, however, cases have been reported in increasing number, and over 60 cases have now been recorded in more or less detail. Most of these have been in the United States, in which the disease is widely distributed from California to Florida, to Maryland, to Minnesota, and in many intermediate states. Cases have also been reported in Java, the Philippines, Argentina, Brazil and Central America. The disease is evidently widely distributed, and probably is much commoner than has been realized.

In many of these cases diagnosis depended entirely upon morphological demonstration of the organisms in tissues at autopsy, but in a number of them (at least nine) the organism has been cultivated from the blood or tissues before or after death, and positively identified.

In the tissues the organisms are found chiefly within large mononuclear phagocytes (reticuloendothelial cells), although extracellular organisms have been observed. There may be only a few organisms within a cell, but often the cells are densely packed with them. The organism is round or oval in outline, usually 3 to 5 micra in diameter, occasionally larger. In stained preparations there is a small, deeply staining mass of chromatin which may appear as a spherical or crescentic body more or less centrally located, surrounded by a clear area and enclosed in a highly refractile capsule which does not take any of the ordinary stains. There is no accessory chromatin dot or kinetoplast such as is found in the Leishman-Donovan bodies of kala azar.

When grown in cultures, the organism appears in two forms. In cultures directly from the body grown on blood agar at 37° C., it appears as yeast-like cells which multiply by budding. In older cultures or those grown at room temperature the yeast-like cells grow out into slender, branching,

[1] DARLING, S. T.: The morphology of the parasite (*Histoplasma capsulatum*) and the lesions of histoplasmosis, a fatal disease of tropical America, Jr. Exper. Med., 1909, xi, 515.

septate mycelia and form white, fluffy, cotton-like colonies with aerial hyphae which bear large spores 8 to 13 micra in diameter at the tips of the branches or stalked along the hyphae. It has been difficult to make the mycelial form revert to the yeast-like form in cultures, but when susceptible animals are infected with cultures in the mycelial stage, the organisms appear in their tissues in the yeast-like form.

The organism was first cultivated by DeMonbreun [2] from the blood of an infant with a disseminated infection, in whom the diagnosis had been made before death by Dodd and Tompkins [3] by demonstrating the organism in the monocytes in blood films. DeMonbreun was the first to establish the nature of the parasite as a fungus. He produced infection in monkeys, dogs and mice by inoculation of cultures. Redaelli and Ciferri [4] reported successful infection of rabbits and guinea pigs, and Reid et al.[5] infected guinea pigs by intraperitoneal injections. Parsons [6] also infected mice by intravenous injection, producing a disseminated infection similar to that in man.

The lesions in experimental infections in the main closely resemble those in human cases. In the earlier stages of an acute disseminated infection, phagocytes stuffed with parasites may occur in masses or sheets in the organs with little or no evidence of inflammatory reaction. In somewhat later stages, typically small tubercle-like lesions are produced, with a necrotic caseous central area surrounded by granulomatous tissue in which there are many phagocytes containing parasites. In late stages the lesions become fibrosed, and it may be difficult or impossible to find parasites. Such lesions may occur in any organ containing reticuloendothelial cells, particularly in the spleen, liver and deep lymph nodes, and often in the lung. Extensive necroses of the adrenal glands have occurred in a number of cases. There may be ulcerative lesions of the skin, the buccal or laryngeal mucous membrane or of the colon.

Although organisms are found mainly in reticuloendothelial phagocytes, they have also been found in the cells of the adrenal cortex and medulla, the epithelial cells of the liver as well as the Kupffer cells, in glandular epithelium of the larynx, in acinar epithelium of the prostate and rarely in neutrophilic leukocytes.[7]

An excellent review of the clinical and pathological features of the earlier

[2] DeMonbreun, W. A.: Cultivation and cultural characteristics of Darling's *Histoplasma capsulatum*, Am. Jr. Trop. Med., 1934, xiv, 93–125.

[3] Dodd, Katherine, and Tompkins, Edna: A case of histoplasmosis of Darling in an infant, Am. Jr. Trop. Med., 1934, xiv, 127–137.

[4] Redaelli, P., and Ciferri, R.: Etudes sur "l'histoplasma capsulatum" Darling; reproduction expérimentale de l'histoplasmose (etc.), Soc. internaz. de microbiol., Boll. d. sez. ital., 1934, vi, 193–195.

[5] Reid, J. D., et al.: Systemic histoplasmosis; systemic histoplasmosis diagnosed before death and produced experimentally in guinea pigs, Jr. Lab. and Clin. Med., 1942, xxiv, 419–434.

[6] Parsons, R. J.: Experimental histoplasmosis in mice, Arch. Path., 1943, xxiv, 229–239.

[7] Van Pernis, P. A., Benson, M. E., and Holinger, P. H.: Laryngeal and systemic histoplasmosis (Darling), Ann. Int. Med., 1943, xviii, 384–393.

cases was published by Meleney [8] in 1940, and more recently Boltjes [9] has reviewed the subject on the basis of 30 collected cases in which reasonably adequate clinical as well as pathological data were available. The clinical manifestations of the disease vary markedly depending upon the extent and distribution of the lesions and the acuteness of the infection. The disease occurs as a generalized infection running a rapidly progressive course with a fatal outcome within a few weeks or months, particularly in young individuals. In less acute cases, lesions may be predominantly localized in one or a few tissues or organs. Isolated areas of histoplasma infection, particularly in the lungs or adrenal glands, have been described as incidental findings in individuals dying of some other unrelated disease.

The generalized type of infection is characterized by protracted irregular fever, weakness, emaciation, progressive anemia and usually a leukopenia with reduction in the granular leukocytes. The liver and spleen are almost always enlarged, often markedly so, and this is clinically evident in about 80 per cent of the cases. Lymph nodes are enlarged in about two-thirds of the cases, but the deep nodes such as the peribronchial or mesenteric are primarily affected, and notable enlargement of the superficial nodes occurs only occasionally. The parasites have been demonstrated in the monocytes of the circulating blood in several of these cases, and in them the organism has been obtained in blood cultures.[2, 5, 10] In at least five cases organisms have been demonstrated in sternal marrow smears, but negative results have been obtained in some cases. This type of the disease resembles kala azar.

Pulmonary lesions, sometimes with pleural involvement, have been described in about half the cases. In several, such as two reported by Meleney [11] these dominated the clinical picture. These cases resemble chronic tuberculosis, and in several cases there was an associated tuberculosis.

In about one-third of the cases intestinal ulcers have occurred, with parasitized phagocytes in the walls or base of the ulcers. Less frequently there may be a severe chronic diarrhea, suggesting a chronic ulcerative colitis, as in the case of Henderson et al.[12]

In another group the presenting lesions have been chronic granulating ulcers in the buccal or pharyngeal mucous membrane or in the larynx. Van Pernis et al.[7] have reported such a case, associated with extensive lesions in the adrenals and many of the clinical manifestations of Addison's disease. Ulcerative lesions of the skin have also been reported.

[8] MELENEY, H. E.: Histoplasmosis (reticuloendothelial cytomycosis): a review, Am. Jr. Trop. Med., 1940, xx, 603–616.

[9] BOLTJES, B.: Histoplasmosis. Report of a case with brief review of the literature, Jr. Kansas Med. Soc., 1943, xliv, 226–229.

[10] WRIGHT, R. B., and HACHTEL, F. W.: Histoplasmosis of Darling; report of a case, ANN. INT. MED., 1941, xv, 309–319.

[11] MELENEY, H. E.: Pulmonary histoplasmosis; report of two cases, Am. Rev. Tuberc., 1941, xliv, 240–274.

[12] HENDERSON, R. G., PINKERTON, H., and MOORE, L. T.: *Histoplasma capsulatum* as a cause of chronic ulcerative enteritis, Jr. Am. Med. Assoc., 1942, cxviii, 885–889.

Broders et al.[13] have reported one case in which there was a mycotic vegetative endocarditis in a heart previously damaged by rheumatic fever. The diagnosis had been established by biopsy of the liver, but the endocarditis was not recognized until autopsy, when large numbers of parasites were found in the vegetations.

The prognosis in histoplasmosis appears to be unfavorable, since with one exception every case recognized during life has died. Meleney[8] mentioned one patient who was treated with neostam, a pentavalent antimony preparation, because he was thought erroneously to have kala azar, and who made at least a temporary clinical recovery. Thus far, however, only severe progressive cases have been recognized. Unless the disease were suspected and a biopsy carried out, there is at present no means of making a diagnosis in mild cases, if they occur. In the chronic cases there appears to be a definite tendency for the tubercle-like lesions to heal with disappearance of the parasites. It seems probable that some cases recover or become arrested.

The mode of infection is not known, although the skin, the respiratory and gastrointestinal tracts have been suggested as portals of entry. De-Monbreun found a dog naturally infected, and he was able to infect dogs by feeding cultures of histoplasma. Morphologically similar organisms have been found in ferrets and in mice. It is possible, therefore, that man might be infected by such animals. The organism has not been found naturally outside the body.

It is evident from this brief review that histoplasmosis may simulate many types of subacute and chronic infections. It should be considered as a possibility in infections of obscure nature, particularly of the types mentioned. Diagnosis can be established with certainty only by cultivation of the organism, although its morphological appearance is so distinctive as to make possible a diagnosis with a high degree of probability. This may be best accomplished by biopsy of a suspicious lesion if one is accessible. Examination of stained films of the blood and sternal marrow and cultures of the blood should reveal the organisms in many cases of disseminated infection. If these are unsuccessful, puncture or biopsy of the liver or spleen may be carried out. Using as antigen a filtrate of a broth culture, Van Pernis et al.[7] obtained positive intracutaneous reactions in one patient, and in experimentally infected mice, whereas negative reactions were obtained in controls. Further study is required to determine the value of this procedure.

[13] Broders, A. C., et al.: Histoplasmosis producing vegetative endocarditis; review of the literature and report of a case, Jr. Am. Med. Assoc., 1943, cxxii, 489–491.

REVIEWS

A Textbook of Pathology. Fifth Edition. Edited by E. T. Bell, M.D., Professor of Pathology, University of Minnesota. 862 pages; 24 × 15.5 cm. Lea & Febiger, Philadelphia. 1944. Price, $9.50.

The fifth edition of Bell's "Textbook of Pathology" maintains the high standards established in previous editions. This edition includes new material on shock, the vitamin deficiencies, blast injuries, Boeck's sarcoid and certain infectious diseases of military interest. The early chapters deal with toxics of a fundamental pathological nature, whereas later chapters are devoted to the special pathology of the various organs and systems. The textual material is concise, the exposition clear and the bibliographies at the end of each section are brief, but well chosen. Illustrations are uniformly good. The typography and format of the book are excellent. This volume can be heartily recommended to any student of pathology, be he undergraduate or graduate. As a ready reference work in pathology, it should merit a prominent place in the library of the practicing physician.

M. S. S.

Handbook of Nutrition. A Symposium Prepared under the Auspices of the Council on Foods and Nutrition of the American Medical Association. (Reprinted from the Journal of the American Medical Association with Additions.) 579 pages; 14.5 × 22 cm. American Medical Association, Chicago. 1943. Price, $2.50.

The *Handbook of Nutrition* is a comprehensive and concise review of all phases of nutrition and the chemistry and physiology connected with it. It includes much material intended primarily for physicians but also of interest to dietitians. The latest developments in research on vitamins and other dietary factors are here. Each chapter in the book is written by a different author, each outstanding in the fields of nutrition, medicine, or commercial research. Every one is well qualified to write on his subject. It contains a great deal of practical and interesting information and should be very useful as a reference book to both physicians and nutritionists. Abundant reference material is listed in the footnotes all the way through the book. A few of the authors are E. V. McCollum, Professor of Biochemistry at Johns Hopkins University; James S. McLester, Chairman of the Council on Foods and Nutrition of the American Medical Association; H. C. Sherman, Professor of Chemistry, Columbia University; Hazel K. Stiebeling, Assistant Chief, Bureau of Human Nutrition and Home Economics, U. S. Department of Agriculture; Edward F. Kohman, Research Chemist, Campbell Soup Company.

The first eleven chapters are concerned with the specific dietary factors, their functions, the latest results of research on them, the requirement for optimum health, and other pertinent information. The essential amino acids and their nature are discussed at length in the chapter on proteins. It is suggested that certain amino acids may be eliminated from the diet in some pathological conditions but as yet, not enough is known about the subject to make it practical. The best sources of amino acids are still the good animal and vegetable protein foods. The chapter called *Calories in Medical Practice* takes up the calculation of caloric requirement, the way calories should be distributed among the various food groups in the diet, and the use of this energy in the body.

The chapters on vitamins are particularly interesting because there is so much new material on them. The two chapters are *The Fat Soluble Vitamins* and *The Water Soluble Vitamins.* The aim in the discussion of vitamins in this book is to present the latest material. The reader is referred to a symposium on vitamins printed

by the American Medical Association in 1939 for the older basic and fundamental facts about vitamins. A few of the interesting facts given may be mentioned. In general the fat soluble vitamins are stored in much larger quantity than the water soluble ones. Ninety-five per cent of the vitamin A is stored in the liver, and this amount increases with age. A good amount is supplied for the very tiny baby as early human milk has from five to ten times the biologic activity of vitamin A of cow's milk. Since the water soluble vitamins are so little stored, it is very necessary to get the requirement daily. Vitamin K is the vitamin concerned with the amount of prothrombin in the blood and consequently the clotting power. In general, a deficiency of K is observed only in new-born infants. This has been explained as follows. Vitamin K is supplied to the body mainly by bacteria in the intestinal tract rather than in the food. The deficiency in the new-born child occurs because these bacteria have not yet had a chance to develop. Administration of K corrects the condition.

The chapter on Preservation of the Nutritive Value of Foods in Processing is important because of the great amount of food preservation being done now. Improving the Quality of Cheap Staple Foods is interesting as it tells what the government is doing to try to improve the diet of the average person and those with a low income. A table giving the current standards of enrichment and fortification of some foods is given. The foods to which these standards pertain are white flour enriched with thiamin, riboflavin, niacin and iron; oleomargarine with vitamin A; milk with vitamin D; and table salt with iodides. The chapter called Feeding the Aged is enlightening and throws light on a subject which often seems to be neglected. With the elimination and control of many diseases which occur early in life, there are coming to be more and more "older people." In order that they shall not be a liability their vitality must be preserved with the aim "to add life to years rather than years to life," and this is largely a matter of nutrition. Doctors must guide older people in their dietary habits and the essence of this guidance is not in restricting their diets, but in keeping it well balanced with plenty of protein and calories, and a little less fat. The last three chapters are of practical interest mainly to physicians. They are concerned with organic maladies affecting the use of food in the body and physical examinations of patients for malnutrition.

Besides being practical and useful, this book is broadening to the education of both doctors and dietitians.

M. F.

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Analysis and Interpretation of Symptoms. Edited by CYRIL M. MACBRYDE, M.D. (Reprinted from Clinics, April, 1944; Vol. II, No. 6—pages 1343-1644.) 301 pages; 23.5 × 16 cm. 1944. J. B. Lippincott Co., Philadelphia. Price, $4.00.

Physical Medicine in General Practice. By WILLIAM BIERMAN, M.D. 654 pages; 24 × 16 cm. 1944. Paul B. Hoeber, Inc., New York. Price, $7.50.

The Diabetic Life. Its Control by Diet and Insulin. 13th Edition, with war-time supplement. By R. D. LAWRENCE, M.A., M.D., F.R.C.P. (London). 228 pages; 21 × 14 cm. 1944. The Blakiston Company, Philadelphia. Price, $4.00.

Psychiatry and the War. (A Record of the Conference on Psychiatry held at Ann Arbor, Michigan, October 22, 23, and 24, 1942, at the Invitation of the University

of Michigan and McGregor Fund.) Edited by FRANK J. SLADEN, M.D. 505 pages; 23.5 × 16 cm. 1944. Charles C. Thomas, Springfield, Illinois. Price, $5.00.

The International Bulletin for Medical Research and Public Hygiene. Vol. A44—Poliomyelitis—By EDWARD C. ROSENOW, M.D. (Editor-in-Chief: W. L. COLZE.) 87 pages; 23 × 15.5 cm. 1944. From the Mayo Foundation for Medical Education and Research, University of Minnesota, Rochester. Printed by Drechsel Printing Company, New York City.

International Organization for Health. By C.-E. A. WINSLOW, M.D. 32 pages; 21 × 14 cm. 1944. Commission to Study the Organization of Peace, New York City. Price, $.10 (25 or more copies—10% discount).

Bacterial Infection with Special Reference to Dental Practice. 3rd Edition. By J. L. T. APPLETON, B.S., D.D.S., Sc.D. 498 pages; 24 × 15.5 cm. 1944. Lea & Febiger, Philadelphia. Price, $7.00.

The Electrocardiogram. Its Interpretation and Clinical Application. By LOUIS H. SIGLER, M.D., F.A.C.P. 403 pages; 23.5 × 16 cm. 1944. Grune & Stratton, Inc., New York City. Price, $7.50.

Secretory Mechanism of the Digestive Glands. By B. P. BABKIN, M.D., D.Sc., LL.D., F.R.S.C. 900 pages; 24 × 16 cm. 1944. Paul B. Hoeber, Inc., New York City. Price, $12.75.

Principles and Practices of Inhalational Therapy. By ALVAN L. BARACH, M.D. 315 pages; 23.5 × 16 cm. 1944. J. B. Lippincott Co., Philadelphia. Price, $4.00.

Artificial Pneumothorax in Pulmonary Tuberculosis. By T. N. RAFFERTY, M.D. Introduction by HENRY STUART WILLIS, M.A., M.D. 192 pages; 22.5 × 15 cm. 1944. Grune & Stratton, Inc., New York City. Price, $4.00.

Infections of the Peritoneum. By BERNHARD STEINBERG, M.D. With a foreword by FREDERICK A. COLLER, M.S., M.D. 455 pages; 24 × 16 cm. 1944. Paul B. Hoeber, Inc., New York City. Price, $8.00.

Pensamentos. By RENATO KEHL (da Academia de Medicina, Rio de Janeiro e Lima). 29 pages; 16.5 × 12 cm. 1942. Livraria Francisco Alves, Paulo de Azevedo & Cia, Rio de Janeiro.

Hipertension Arterial Nefrogena. By EDUARDO BRAUN-MENENDEZ, JUAN CARLOS FASCIOLO, LUIS F. LELOIR, JUAN M. MUÑOZ, and ALBERTO C. TAQUINI. 475 pages; 23 × 16 cm. 1943. El Ateneo, Buenos Aires.

Cancer Primitivo del Pulmon. Estudio Clinico Quirurgico. By ERNESTO ESCUDERO. 542 pages; 23 × 16 cm. 1943. Libreria Hachette S. A., Buenos Aires.

Medical Education in the United States before the Civil War. By WILLIAM FREDERICK NORWOOD, Associate Professor of the History of Medicine and Associate Dean in the School of Medicine, College of Medical Evangelists, Los Angeles. Foreword by HENRY E. SIGERIST. 487 pages; 24 × 16 cm. 1944. University of Pennsylvania Press, Philadelphia. Price, $6.00.

COLLEGE NEWS NOTES

Additional A. C. P. Members in the Armed Forces

Previously reported in the News Notes section of this journal were the names of 1,071 Fellows and Associates of the College on active military duty. The following additional members have since reported for active duty, bringing the total to 1,706.

William L. Cover
Albert C. Santy
Laurance W. Kinsell
Frederick Steigmann
Morgan Y. Swirsky

Major Robert E. Lyons, Jr., (MC), AUS—honorably discharged October 8, 1943.

New Life Member

Dr. Harold H. Jones, F.A.C.P., Winfield, Kan., became a Life Member of the College on June 24, 1944.

Gifts to the College Library

The following gifts are gratefully acknowledged:

Books

Dr. Louis H. Sigler, F.A.C.P., Brooklyn, N. Y.—"The Electrocardiogram, Its Interpretation and Clinical Application."
Dr. Carl J. Wiggers, F.A.C.P., Cleveland, Ohio—"Collected Papers from the Department of Physiology, Western Reserve University School of Medicine—Volume X, Studies on Shock."

Reprints

J. Edward Berk, F.A.C.P., Captain, (MC), AUS—1 reprint.
Charles A. Bohnengel, F.A.C.P., Captain, (MC), AUS—1 reprint.
Dr. Alexander G. Davidson, F.A.C.P., Brooklyn, N. Y.—2 reprints.
Arden Freer, F.A.C.P., Colonel, (MC), USA—1 reprint.
Dr. I. W. Held, F.A.C.P., New York, N. Y.—1 reprint.
Irving R. Juster, F.A.C.P., Major, (MC), AUS—1 reprint.
Morgan Y. Swirsky, (Associate), Lieutenant, (MC), AUS—3 reprints.
Leon H. Warren (Associate), Lieutenant Colonel, (MC), AUS—1 reprint.
Dr. Mast Wolfson, F.A.C.P., Monterey, Calif.—1 reprint.
Dr. Edwin E. Ziegler, F.A.C.P., Bethlehem, Pa.—1 reprint.

Communication from the Royal College of Physicians, Pall Mall East, S. W. 1, London:

"22nd May, 1944

Dear Sir:

I think it would be a very good idea if you would announce in the Annals of Internal Medicine the fact that Fellows of the American College of Physicians will be welcome to lectures at this College. We advertise these lectures in the *Lancet*, *British Medical Journal* and the British *Times* newspaper, so that anyone interested can inform himself of the title and date. I think, therefore, that these arrangements will cover it for the immediate future.

I was very interested to meet Colonel (William S.) Middleton the other day, when we were delighted to admit him a Fellow of this College. I first met him in France during the last War. We spoke together of this subject, and he said that he would like to help in making members of your College now in this Country, aufait with our invitation.

Yours truly,

(Signed) H. E. A. BOLDERO
Registrar

To The Executive Secretary, The American College of Physicians"

HARVARD MEDICAL SCHOOL ENCOURAGES STUDY OF LEGAL MEDICINE

Dr. Frank R. Ober, Assistant Dean of Harvard Medical School, recently announced that the graduate department with the coöperation of the Medical Schools of Boston University and Tufts College has planned a condensed one-day conference and a more extensive seminar in legal medicine. No attempt will be made to turn out medico-legal specialists, but the object is to give to the average medical examiner, coroner, or other physician interested in the subject, a clearer, general working knowledge, in order that he can better perform his day-to-day duties.

The Massachusetts Medico-Legal Society, in conjunction with the aforementioned institutions, has arranged for an all-day Conference, to be held at the Mallory Institute of Pathology, Boston City Hospital, Wednesday, October 4, 1944. It will include lectures, demonstrations and informal discussions concerning many subjects in legal medicine, particularly stressing some of the more recent procedures. There will be no registration fee, and the meeting will be open to any registered physician, lawyer, police official, senior medical student, or other medical investigator who may be interested. Advance application is not essential, but it will be helpful to those arranging the Conference if notice of intention to attend is sent prior to October 1 to Dr. W. H. Watters, Department of Legal Medicine, Harvard Medical School, Boston.

The Seminar in legal medicine will be given at Harvard Medical School, Courses for Graduates, during the entire week of October 2–7. It is planned particularly for medical examiners and coroners' physicians, but will be open to any suitable graduate of an approved medical school. The course will be practical rather than theoretical, and will consist of autopsy demonstrations, technique and interpretation of laboratory tests, study of the day-by-day cases of a medical examiner, round table conferences and many other subjects included within the widening field of legal medicine. The Seminar fee is $25.00, and enrollment will be limited to fifteen applications, which should be filed before October 1, with Harvard Medical School, Courses for Graduates, 25 Shattuck Street, Boston 15, Mass.

PHYSICIAN-ARTISTS' PRIZE CONTEST

The American Physicians Art Association, with the coöperation of Mead Johnson & Company, is offering an important series of War Bonds as prizes to physicians in the Armed Services and also physicians in civilian practice for their best artistic works depicting the medical profession's "skill and courage and devotion beyond the call of duty."

Announcement of further details will be made soon by the Association's Secretary, Dr. F. H. Redewill, Flood Building, San Francisco, Calif.

In the June, 1944, number of the ANNALS OF INTERNAL MEDICINE, page 1009, was published the names of the members of the College from the United States who attended the inaugural meeting of the new National Institute of Cardiology at Mexico City, as guests of the Mexican Government. From this list was inadvertently omitted the name of Dr. Joseph Kopecky, F.A.C.P., of San Antonio, Texas. We regret the omission.

The New York Institute of Clinical Oral Pathology announces its first open meeting to be held at the New York Academy of Medicine, October 30, 1944, in Hosack Hall. The symposium will be devoted to "Fluorine and Dental Caries." Members of the medical, dental and public health and other professional groups are cordially invited. Further information is available through the Executive Secretary, 101 E. 79th Street, New York 21, N. Y.

Dr. Roger I. Lee, F.A.C.P., former President of the American College of Physicians, of Boston, has been elected President-Elect of the American Medical Association, and will be inducted to the Presidency at the New York meeting of that society next year.

Dr. A. C. Ivy, F.A.C.P., Dr. J. A. Roth and Dr. A. J. Atkinson, of Northwestern University Medical School, Chicago, were awarded the bronze medal in Group I of the scientific exhibits of the American Medical Association at Chicago during June. Their exhibit dealt with the effect of caffein on the formation of ulcers.

Dr. George Dock, F.A.C.P., Los Angeles, Calif., was the recipient of the Distinguished Service Medal of the House of Delegates of the American Medical Association for 1944. Dr. Dock is noted for his work on the pathology of malaria and dysentery, protozoan diseases of the blood, pernicious anemia, the ductless glands and hookworm.

From nominations submitted to the Committee on Distinguished Service Award, five names are selected and passed on to the Board of Trustees, which in turn selects three for submission to the House of Delegates. The three names presented for 1944 were those of Dr. Isaac A. Abt, of Chicago, Dr. George Dock, of Los Angeles and Dr. Simon Flexner, of New York.

MINNEAPOLIS PUBLIC LIBRARY STAGES A MEDICAL ART SHOW

The Minneapolis Public Library, from June 21 to July 22, staged an unique art show, representing the work of leading medical artists the country over. It is part of a program for extending the services of the Public Library to one of the important medical centers in the United States. A display of rare medical books and prints formed an important part of the exhibit. The Surgeon General's Office in Washington supplied four books showing the earliest examples of anatomical drawings. A copy of the 1783 Vesalius from the library of Dr. Shirley Miller of the University of Minnesota, and photostatic copies of early anatomies were on display.

Captain William Stein, (MC), AUS, (Associate), formerly of New Brunswick, N. J., has been made the Chief of the Medical Services of the 313th Station Hospital overseas.

Dr. Burrell O. Raulston, F.A.C.P., Los Angeles, Calif., has been appointed by the Section on the Practice of Medicine of the American Medical Association a member of the American Board of Internal Medicine, effective July 1, 1944, succeeding Dr. Ernest E. Irons, F.A.C.P., Chicago, who has served as Chairman of the Board for some years.

Dr. Reginald Fitz, F.A.C.P., Boston, has been appointed Chairman. Other additions to the Board include Dr. Frederic M. Hanes, F.A.C.P., Durham, N. C., and Dr. Cecil J. Watson, F.A.C.P., Minneapolis, Minn., both appointees of the American College of Physicians.

Colonel Howard A. Rusk, (MC), U. S. Army, F.A.C.P., formerly of St. Louis, recently received an award of $1,000.00 for outstanding contributions to the rehabilitation of the war injured. The presentation was made at the Lord and Taylor Seventh Annual American Design Awards luncheon at the Waldorf-Astoria, New York City, on April 20. Colonel Rusk is now Chief of the Convalescent Branch, Office of the Air Surgeon, Washington, D. C.

Dr. J. Q. Griffith, F.A.C.P., Philadelphia (with Wilfred Fry) received a certificate of merit for an exhibit on "choked disk" at the meeting of the American Medical Association in Chicago during June.

Dr. Julius H. Comroe, Sr., F.A.C.P., York, Pa., recently received the Civilian Service Award in recognition of his faithful service as Chief of the Cardiac Specialists at the Harrisburg Armed Forces Induction Center. Dr. Comroe, during the past two years and seven months devoted over 690 days to the examination of selectees.

Dr. J. Winthrop Peabody, F.A.C.P., Washington, D. C., has been elected an Honorary Member of the Sociedad Chilena de Tisologia.

Dr. Jay Arthur Myers, F.A.C.P., Minneapolis, Minn., was inducted as President of the American College of Chest Physicians at its tenth annual meeting in Chicago, June 10–12, 1944. Major General Shelley U. Marietta, F.A.C.P., Washington, D. C., was elected Second Vice President.

Dr. B. P. Seward, F.A.C.P., Roanoke, Va., has been elected a Vice President of the Roanoke Academy of Medicine.

Dr. Anthony Bassler, F.A.C.P., New York City, showed a moving picture on "Treatment of Intestinal Amebiasis" before the recent meeting of the National Gastroenterological Association in New York, June 7. Dr. Linn J. Boyd, F.A.C.P., New York City, gave a paper on "Liver Function Tests: A Study of 600 Cases." Dr. Hyman I. Goldstein (Associate), Camden, N. J., discussed "Post-War Malaria," a paper presented before the meeting by Dr. Isidore Snapper.

The twenty-second annual fall clinical conference of the Kansas City Southwest Clinical Society will be held at Kansas City, October 2–3–4, 1944. Among the guest speakers will be Dr. Russell L. Haden, F.A.C.P., Cleveland, and Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor.

Dr. Benjamin M. Bernstein, F.A.C.P., Brooklyn, delivered a paper before the Section on Gastro-enterology and Proctology of the American Medical Association at Chicago, June 14, on "Gastro-duodenal Dyssynergia."

Dr. Benjamin W. Black, F.A.C.P., Oakland, Calif., was chairman at ceremonies at which Cutter Laboratories, Berkeley, Calif., were awarded the Army-Navy E pennant for outstanding achievement in war production. Dr. Black asserted that Cutter Laboratories' production of blood plasma, vaccines and penicillin is unequaled in the world.

Dr. Francis G. Blake, F.A.C.P., Regent of the College and Dean of Yale University School of Medicine, will be the chairman of the twentieth clinical congress of postgraduate medicine of the Connecticut State Medical Society, New Haven, September 28–29.

Dr. Gerardo M. Balboni, F.A.C.P., Boston, was recently appointed a member of the Massachusetts State Board of Registration in Medicine.

Dr. Benjamin A. Shepard, F.A.C.P., Kalamazoo, recently retired because of ill health as Medical Director of the Pine Crest Sanatorium, Oshtemo, Mich. The Sanatorium has been taken over by the State Sanatorium Commission and will be known as the Pine Crest State Sanatorium.

Dr. Edgar E. Evans (Associate), Penns Grove, N. J., addressed the New Jersey Association of Industrial Physicians at Newark, June 30, on "Hydrofluoric Acid Burns and Their Treatment."

Dr. Strecker Receives Strittmatter Award

Dr. Edward A. Strecker, F.A.C.P., Professor of Psychiatry and Chairman of the Department, University of Pennsylvania School of Medicine, recently was awarded the Strittmatter Award of the Philadelphia County Medical Society "in recognition of his distinguished service in the field of psychiatry and mental hygiene and his unselfish devotion to the highest ideals of the profession as physician, teacher, author and consultant in civilian and military medicine."

Colonel Pincoffs Receives Legion of Merit Award

Colonel Maurice C. Pincoffs, F.A.C.P., Regent of the College and Editor of the Annals of Internal Medicine, formerly Professor of Medicine at the University of Maryland School of Medicine and now Chief of Professional Services of the Southwest Pacific area, was recently awarded the Legion of Merit for experimental work in malaria control. Colonel Pincoffs has been on active service since April 20, 1942.

Civilian Consultants Named as Advisers to the Army Medical Department

Nineteen civilian specialists have been recently appointed as a board of advisers to the Office of the Surgeon General. Among these appointees are Dr. Walter L.

Palmer, F.A.C.P., Chicago, and Dr. Chester M. Jones, F.A.C.P., Boston, (gastro-enterology); Dr. Paul D. White, F.A.C.P., Boston, and Dr. Robert L. Levy, F.A.C.P., New York, (heart disease); Dr. Chester S. Keefer, F.A.C.P., Boston, (chemotherapy); Dr. Francis M. Rackemann, F.A.C.P., Boston, and Dr. Robert A. Cooke, F.A.C.P., New York, (allergy); Dr. James J. Waring, F.A.C.P., Denver, and Dr. J. Burns Amberson, Jr., F.A.C.P., New York, (tuberculosis).

Dr. Hugh B. Campbell, F.A.C.P., Norwich, is Treasurer of the Connecticut State Medical Society. Dr. Campbell recently resigned as Superintendent of the Norwich State Tuberculosis Sanatorium, Uncas-on-Thames, to become Medical Director of the Phoenix Life Insurance Company of Hartford. He has been succeeded by Dr. William H. Weidman, F.A.C.P., who heretofore has been Senior Sanatorium Physician.

Dr. Arthur C. Christie, F.A.C.P., Washington, D. C., has retired from the faculty of Georgetown University School of Medicine as special lecturer in medical economics, but retains his position as Professor of Clinical Radiology. The Executive Secretary of the Medical Society of the District of Columbia, Mr. Theodore Wiprud, has been appointed Professor of Medical Socio-economics, succeeding Dr. Christie.

At its fourth annual meeting, Chicago, June 11, the American Diabetes Association initiated and made awards of the Banting Memorial Medal to all ex-presidents and to all lecturers of the Association. The medal memorializes Sir Frederick Banting, F.A.C.P., discoverer of insulin, who at the time of his death was the honorary president of the American Diabetes Association. Among those receiving the medals were Dr. Cecil Striker, F.A.C.P., Cincinnati; Dr. Herman O. Mosenthal, F.A.C.P., New York; Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia; Dr. Elliott P. Joslin, F.A.C.P., Boston; and Col. Leonard G. Rowntree, (MC), AUS, F.A.C.P.

Two medals will be awarded annually in the future—one to the outgoing president and one to the lecturer.

Dr. Joseph H. Barach, F.A.C.P., Pittsburgh, was elected the new president and Drs. Russell M. Wilder, F.A.C.P., Rochester, Minn., and Edward S. Dillon, F.A.C.P., Philadelphia, were elected vice presidents. Dr. Cecil Striker was reëlected secretary.

At the annual meeting of the American Gastro-enterological Association at Chicago, June 13, Dr. A. H. Aaron, F.A.C.P., Buffalo, was elected president; Drs. Henry L. Bockus, F.A.C.P., Philadelphia, and Walter L. Palmer, F.A.C.P., Chicago, vice presidents; Dr. John G. Mateer, F.A.C.P., Detroit, treasurer; and Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., secretary. The next annual meeting will be held in Atlantic City, May, 1945.

Dr. Stanley P. Reimann, F.A.C.P., Philadelphia, was recently elected president-elect of the American Society of Clinical Pathologists. Dr. J. J. Moore, F.A.C.P., Chicago, was reëlected vice president.

Dr. Ellen C. Potter, F.A.C.P., Director of Medicine, New Jersey State Department of Institutions and Agencies, Trenton, was made president of the National Conference on Social Work, May 27.

Dr. William H. Perkins, F.A.C.P., Dean and Professor of Preventive Medicine, Jefferson Medical College, Philadelphia, addressed the New Castle County Medical Society and the Delaware Academy of Medicine at Wilmington, Del., May 16, on "Tropical Diseases of Concern to the Home Front."

Dr. William Cabell Moore, F.A.C.P., Washington, D. C., has retired as Medical Director of the Chesapeake and Potomac Telephone Company, a position he has held since March, 1922, and will be succeeded by Dr. R. Lomax Wells, F.A.C.P., Washington, D. C.

Dr. Robinson Bosworth, F.A.C.P., East St. Louis, Ill., received the Dearholt Medal of the Mississippi Valley Conference on Tuberculosis, May 10. Dr. Bosworth is Medical Director of Pleasant View Sanatorium. The citation accompanying the medal referred to his contribution to the development of sanatoriums for the treatment of tuberculosis and declared him "a pioneer in the development of standards for outpatient work."

On May 22, members of the Chicago Society of Internal Medicine elected Dr. Lee C. Gatewood, F.A.C.P., as president and Dr. George E. Wakerlin, F.A.C.P., vice president.

The Medical Society of the State of North Carolina, at its recent annual meeting, installed Dr. Paul F. Whitaker, F.A.C.P., Kinston, as president and elected Dr. William H. Smith, F.A.C.P., Goldsboro, a vice president.

Dr. Sidney A. Slater, F.A.C.P., Worthington, Minn., has served six years as president of the Minnesota Public Health Association. Recently the Association presented him with a gold wrist watch as a token of appreciation and recognition.

Dr. Howard K. Petry, F.A.C.P., Harrisburg, has been appointed Chairman of a board to survey Pennsylvania State institutions for the care of the mentally ill.

State of Washington Considers New Medical School

The Washington State Medical Association has appointed a Committee of which Dr. George H. Anderson, F.A.C.P., Spokane, and Dr. David C. Hall, F.A.C.P., Seattle, are members to study the feasibility of establishing a medical school in connection with the University of Washington at Seattle.

Two Fellows Promoted to Rank of Brigadier General, U. S. Army

Colonel George B. Foster, Jr., F.A.C.P., and Colonel Henry C. Dooling, F.A.C.P., were recently advanced to the rank of Brigadier General in the Medical Corps of the United States Army. Both are members of the "regular" corps.

Dr. Reginald Fitz, F.A.C.P., Boston, Regent of the College, was elected president elect of the Massachusetts Medical Society during its last annual meeting, May 22-24.

The New York Diabetes Association is conducting for the ninth consecutive season, a camp (Camp Nyda) for diabetic boys and girls at Walkill, N. Y. Dr. Frederick W. Williams, F.A.C.P., is in charge of the medical department.

Dr. Mary Riggs Noble, F.A.C.P., Bowmansdale, Pa., is treasurer of the American Medical Women's Association.

New officers of the American Therapeutic Society elected at its Chicago meeting, June 10, include Dr. Edward Sterling Nichol, F.A.C.P., Miami, Fla., president; Drs. Thomas J. Coogan, F.A.C.P., Chicago, Ill., and Charles L. Hartsock, F.A.C.P., Cleveland, Ohio, vice presidents; Dr. Oscar B. Hunter, F.A.C.P., Washington, D. C., secretary.

Dr. R. Finley Gayle, Jr., F.A.C.P., Richmond, Va., has been elected to the Council of the American Psychiatric Association.

Dr. Robert H. Riley, F.A.C.P., Baltimore, Md., has been made Chairman of the Maryland Postmortem Examiners Commission. Dr. Riley is Director of the State Department of Health.

The Alumni Association of the Medical College of the State of South Carolina has established a lectureship to honor Dr. Robert Wilson, Sr., F.A.C.P., recently retired Dean.

On the fifth morning of the American College of Physicians' graduate course given last April at the Massachusetts General Hospital. Dr. Alpheus F. Jennings of Detroit asked for the floor. The doctors, said he, had found the course interesting and particularly they liked the approach, namely, that of resting clinical practice squarely on a sound scientific foundation. As a material token of their satisfaction the doctors asked the Hospital to accept a purse which they had made, and devote it to some purpose of research. It contained three hundred and ten dollars.

This purse was accepted. To this sum has been added the balance of the tuition fees, after expenses had been paid, making a total of one thousand one hundred and two dollars and fifty-nine cents. This has been turned over to the Treasurer of the Massachusetts General Hospital to be held as a special fund—the "ACP Fund." It will be used toward the salary of, or travel for, some young investigator or investigators of promise, probably after demobilization has begun.

Those participating in conducting the course and the American College of Physicians as a whole are very grateful to the doctors taking the course for their gracious action.

Dr. Arthur P. Richardson, Head of the Department of Pharmacology of the University of Tennessee, has been appointed Head of the Division of Pharmacology of the Squibb Institute for Medical Research, to become effective on October 1, 1944. Dr. Richardson will replace Dr. H. B. VanDyke, who has accepted the position as Head of the Department of Pharmacology, College of Physicians and Surgeons, Columbia University.

Dr. Richardson is a native of Longmont, Colorado, but obtained his A.B. and M.D. degrees at Stanford University (California) in '32 and '37 respectively. While taking his doctoral degree, he was assistant in pharmacological research ('33–'36),

and then remained at Stanford as instructor in Pharmacology ('37–'38), and later as assistant professor ('39–'41). He spent a year as National Research Council Fellow at Johns Hopkins ('38–'39). He then became visiting associate professor at the University of Tennessee Medical School, Memphis, Tennessee ('41), where he has since remained as associate professor ('41–'43), professor ('43–) and head of the department ('41–).

Dr. Richardson's chief interests have been in the field of chemotherapeutic research, and he has had very extensive experience in studies concerning malaria and other tropical diseases. For the past two years he has been primarily engaged in the study of antimalarial compounds.

Examinations by Certifying Boards

American Board of Internal Medicine, William A. Werrell, M.D., Assistant Secretary-Treasurer, 1301 University Avenue, Madison 5, Wisconsin.

Written Examinations: October 16, 1944, in various centers throughout the United States; also available to candidates in military and naval services at certain of their stations, with permission of their medical commanding officers. All applications for civilian candidates should be filed by August 15, 1944. Every effort will be made to accommodate candidates in the Service, regardless of the closing date for the acceptance of applications.

Oral Examinations: Consult Assistant Secretary-Treasurer; oral examinations will probably be given just preceding the annual meeting of the American College of Physicians in the early spring of 1945, and also just preceding the annual meeting of the American Medical Association in the late spring of 1945. If the Board finds it possible to conduct regional examinations during 1944, an announcement will appear in the Annals of Internal Medicine and the Journal of the American Medical Association.

American Board of Dermatology and Syphilology, C. Guy Lane, M.D., Secretary, 416 Marlboro Street, Boston, Massachusetts.

Consult the Secretary concerning examination schedule for autumn of 1944 and spring of 1945.

American Board of Pediatrics, C. A. Aldrich, M.D., Secretary, 115½ First Avenue, S. W., Rochester, Minnesota.

Written Examination: September 22, 1944, locally under monitors.

Oral Examinations: St. Louis, Missouri, November 8–9, 1944, and New York City, December 15–16, 1944. Closing date for filing applications, August 15, 1944.

American Board of Pathology, F. W. Hartman, M.D., Secretary-Treasurer, Henry Ford Hospital, Detroit, Michigan.

Consult the Secretary-Treasurer for future schedule.

American Board of Psychiatry and Neurology, Walter Freeman, M.D., Secretary, 1028 Connecticut Avenue, N. W., Washington, D. C.

Consult the Secretary for future schedule. At last advice, this Board will schedule an examination in New York City about the middle of December, 1944. However, the dates for both the written and oral examinations will not be set until late autumn or early winter.

AMERICAN BOARD OF RADIOLOGY, B. R. Kirklin, M.D., Secretary, Mayo Clinic, Rochester, Minnesota.

This Board conducts only a general oral examination. Next examination, Chicago, Illinois, September 22–23–24, 1944.

A. C. P. POSTGRADUATE COURSES

Consult the inside back cover for complete schedule of courses to be offered during the autumn of 1944.

The detailed Bulletin, descriptive of all courses, will be printed during August and distributed about September 1. However, reservations may be entered through the Executive Offices of the College at any time.

The full details of the course in Cardiology, being complete when this issue goes to press, are hereunder published.

COURSE NO. 1—CARDIOLOGY

(October 2–7, 1944)

MASSACHUSETTS GENERAL HOSPITAL

Boston, Mass.

PAUL D. WHITE, M.D., F.A.C.P., *Director*

(Minimal Registration 30; Maximal Registration 50)

OFFICERS OF INSTRUCTION

Donald G. Anderson, M.D., Research Fellow in Medicine, Evans Memorial and Massachusetts Memorial Hospitals; Instructor in Medicine, Boston University School of Medicine.

Joseph C. Aub, M.D., Physician, Massachusetts General Hospital; Director of Medical Laboratories of the Collis P. Huntington Memorial Hospital of Harvard University at the Massachusetts General Hospital; Professor of Research Medicine, Harvard Medical School.

William B. Breed, M.D., F.A.C.P., Physician, Massachusetts General Hospital; Visiting Physician, House of the Good Samaritan; Associate in Medicine, Harvard Medical School.

C. Sidney Burwell, M.D., F.A.C.P., Research Professor of Clinical Medicine and Dean, Harvard Medical School.

Benjamin Castleman, M.D., Acting Director of Department of Pathology and Bacteriology, Massachusetts General Hospital; Instructor in Pathology, Harvard Medical School.

Mandel Cohen, M.D., Assistant Psychiatrist, Massachusetts General Hospital; Instructor in Psychiatry, Harvard Medical School.

Lewis Dexter, M.D., Associate in Medicine, Peter Bent Brigham Hospital; Instructor in Medicine, Harvard Medical School.

Robert E. Gross, M.D., F.A.C.S., Associate Visiting Surgeon, Children's Hospital; Associate in Surgery, Peter Bent Brigham Hospital; Assistant Professor of Surgery, Harvard Medical School.

Burton E. Hamilton, M.D., F.A.C.P., Cardiologist, Boston Lying-In Hospital and New England Deaconess Hospital; Clinical Associate, Thorndike Memorial Laboratory, Boston City Hospital.

T. Duckett Jones, M.D., Director of Research, House of the Good Samaritan; Assistant Physician, Massachusetts General Hospital; Assistant Professor of Medicine, Harvard Medical School.

Otto Krayer, M.D., Associate Professor of Comparative Pharmacology and Head of Department, Harvard Medical School.

Eugene M. Landis, M.D., F.A.C.P., Higginson Professor of Physiology, Harvard Medical School.

Samuel A. Levine, M.D., F.A.C.P., Physician, Peter Bent Brigham Hospital; Assistant Professor of Medicine, Harvard Medical School.

Robert R. Linton, M.D., F.A.C.S., Associate Visiting Surgeon, Massachusetts General Hospital; Instructor in Surgery, Harvard Medical School.

Benedict Massell, M.D., Assistant in Medicine, Massachusetts General Hospital; Visiting Physician, House of the Good Samaritan; Assistant in Medicine, Harvard Medical School.

Sylvester McGinn, M.D., Lieutenant Commander, (MC), USNR, Assistant in Medicine, Massachusetts General Hospital; Assistant in Medicine, Harvard Medical School.

James H. Means, M.D., F.A.C.P., Chief of the Medical Services, Massachusetts General Hospital; Jackson Professor of Clinical Medicine, Harvard Medical School.

Joseph E. F. Riseman, M.D., Associate Visiting Physician, Beth Israel Hospital; Associate in Medicine, Harvard Medical School.

Reginald H. Smithwick, M.D., F.A.C.S., Associate Visiting Surgeon, Massachusetts General Hospital; Instructor in Surgery, Harvard Medical School.

Merrill C. Sosman, M.D., Roentgenologist-in-Chief, Peter Bent Brigham Hospital; Clinical Professor of Roentgenology, Harvard Medical School.

Howard B. Sprague, M.D., F.A.C.P., Captain, (MC), USNR, Associate Physician, Massachusetts General Hospital; Visiting Physician, House of the Good Samaritan; Instructor in Medicine, Courses for Graduates, Harvard Medical School.

Richard H. Sweet, M.D., F.A.C.S., Associate Visiting Surgeon, Massachusetts General Hospital; Instructor in Surgery, Harvard Medical School.

James C. White, M.D., F.A.C.S., Captain, (MC), USNR, Chief of Neurosurgical Service, Massachusetts General Hospital; Assistant Professor of Surgery, Harvard Medical School.

Paul D. White, M.D., F.A.C.P., Physician, In Charge of Cardiac Clinics and Laboratory, Massachusetts General Hospital; Lecturer in Medicine, Harvard Medical School.

Conger Williams, M.D., Assistant in Medicine, Massachusetts General Hospital; Visiting Physician, House of the Good Samaritan; Assistant in Medicine, Courses for Graduates, Harvard Medical School.

This course in the diagnosis and treatment of cardiovascular disease has been arranged to give in one week a summary of the recent advances and present status of our knowledge of cardiovascular disease with particular emphasis on clinical aspects. Some attention is directed also to the fundamental principles of cardiovascular anatomy, physiology, pharmacology and pathology. Authorities in their respective fields who are available to take part have been enlisted, including a number of physicians who have made important contributions to our knowledge of cardiovascular disease. Illustrative cases will be presented. The course will be limited to fifty.

Outline of Course

Monday, October 2.

A.M. Session

9:00–10:00 Anatomy of the Heart and Great Vessels.
Dr. White.

10:00–11:00 Practical Considerations in Cardiovascular Physiology.
Dr. Landis.

11:00–12:00 Cardiovascular Pharmacology.
Dr. Krayer.

12:00– 1:00 Electrocardiography.
Dr. White.

P.M. Session

2:00– 3:00 Precordial Leads in Electrocardiography.
Dr. Williams.

3:00– 4:00 Cardiovascular Roentgenology.
Dr. Sosman.

4:00– 5:00 Case Problems in Cardiovascular Roentgenology.
Dr. White.

Tuesday, October 3.

A.M. Session

9:00–10:00 Cardiovascular Symptoms.
Dr. White.

10:00–11:00 Cardiac Auscultation.
Dr. Levine.

11:00–12:00 Blood Pressure, Normal and Abnormal.
Dr. Dexter.

12:00– 1:00 Peripheral Circulation—Anatomy and Physiology.
Dr. Linton.

P.M. Session

2:00– 3:30 Cardiovascular Pathology.
Dr. Castleman.

3:30– 5:00 Case Problems in Cardiovascular Pathology.
Dr. White.

Wednesday, October 4.

A.M. Session

9:00–11:00 Congenital Heart Disease with Cases.
Dr. White.

11:00– 1:00 Rheumatic Fever and Rheumatic Heart Disease, with Cases.
Dr. Jones and Dr. Massell.

P.M. Session

2:00– 3:00 Cardiovascular Syphilis.
Dr. Hamilton.

3:00– 4:00 Hypertensive Heart Disease.
Dr. White.

4:00– 5:00 The Cor Pulmonale, Acute and Chronic.
Dr. McGinn.

Thursday, October 5.

A.M. Session

9:00–11:00 Coronary Heart Disease.
Dr. Sprague.

11:00–12:00 Medical Grand Rounds. Cardiac Cases.
Dr. Means and Dr. Breed.

12:00– 1:00 Clinicopathological Conference. Cardiovascular Cases.

P.M. Session

2:00– 3:00 Subacute Bacterial Endocarditis.
Dr. Anderson.

3:00– 4:00 Pericarditis, Acute and Chronic.
Dr. Burwell.

4:00– 5:00 Diseases of Arteries and Veins.
Dr. Linton.

Friday, October 6.

A.M. Session

9:00–10:00 Congestive Heart Failure. Diagnosis.
Dr. White.

10:00–11:00 Congestive Heart Failure. Treatment.
Dr. Williams.

11:00–12:00 Arrhythmias. Diagnosis.
Dr. Levine.

12:00– 1:00 Arrhythmias. Treatment.
Dr. Williams.

P.M. Session

2:00– 3:00 Shock.
Dr. Aub.

3:00– 4:00 Neurocirculatory Asthenia.
Dr. Cohen.

4:00– 5:00 Special Notes on Cardiovascular Drugs.
Dr. Riseman.

5:00– 6:00 Motion Picture, "Angina Pectoris."
Dr. Riseman.

Saturday, October 7.

A.M. Session

9:00–12:00 Cardiovascular Surgery.
Dr. White, Dr. Smithwick, Dr. Gross and Dr. Sweet.

12:00– 1:00 Concluding Exercise. The Future of Cardiovascular Disease.
Dr. White.

War-Time Graduate Medical Meetings

Region No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Jolliffe, Dr. H. W. Cave.

Rhoads General Hospital, Utica, New York

August 17 Wounds of the Extremities and Their Management. Dr. Roscoe Severance

Note: Program has been arranged by Capt. J. Edward Berk of this installation.

Region No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole.

Mayo General Hospital, Galesburg, Illinois

Sept. 6 Arthritis { Rheumatoid—Acute Rheumatic Fever / Osteo-arthritis
a. Other bone diseases

Camp Ellis, Illinois

Sept. 6 Laboratory Diagnosis—and its relationship to treatment
a. Hypoproteinemia—Alkalosis—Acidosis—Dehydration—Electrolytic balance

Camp McCoy, Wisconsin

Sept. 6 Orthopedic Problems of General Interest
a. Low back pain—Foot and Knee Strain—March Fracture, etc.

Camp Grant, Illinois

Sept. 6 Symposium on Organic Neurology
a. Central and Peripheral

Truax Field, Wisconsin

Sept. 6 Psychiatry—Psychoneurosis—Neurocirculatory Asthenia—Malingering, etc.

Chanute Field, Rantoul, Illinois

Sept. 6 Peptic Ulcer and Gastritis
a. Diagnosis and medical care
b. Surgical approach

Correction in Announcement re Royal College of Physicians

In the May, 1944, issue of this journal announcement was made of the invitation from the Registrar of the Royal College of Physicians, Pall Mall East, S.W. 1, London, to members of the American College of Physicians to attend the advanced Lectures of the Royal College, given each month from November to July. The announcement should have referred specifically to *Fellows* of the American College of Physicians, because facilities at the Royal College are inadequate at the present time to accommodate also Associates of the American College of Physicians.

Fellows of the American College of Physicians desiring to have their names placed on the mailing list for such invitations may communicate their desires to Dr. G. A. Pemberton Wright, Royal London Ophthalmic Hospital, (Moorfields Eye Hospital), City Road, E. C. 1, London, who will be glad to certify such Fellows to the Registrar of the Royal College of Physicians. It is, of course, important that Fellows, when writing to Dr. Wright, include their mailing addresses.

OBITUARIES

COLONEL PATRICK S. MADIGAN

Colonel Patrick S. Madigan, 57, an officer of the Regular Army Medical Corps for 27 years, died May 8, 1944, at Fort Belvoir, Va., where he was on duty as commanding officer of the station hospital. Burial was in Arlington National Cemetery.

Colonel Madigan was born in Washington, D. C., Feb. 18, 1887. He was graduated from Georgetown University College of Liberal Arts in 1908 and from the medical college of the University in 1912, serving as a member of the Georgetown faculty from 1913 to 1917. He held the degree of Master of Arts and the honorary degree of Doctor of Laws and Letters from Gonzaga College.

Colonel Madigan began his Army medical career as a first lieutenant in the Medical Corps of the Regular Army in 1917 and served in France with the 7th Division, 6th Infantry.

Following the Armistice he returned to this country and for several months was stationed at Hampton Roads, Va. From 1920 until 1926 he was chief of the neuropsychiatry section at the Walter Reed General Hospital in Washington, and during that period studied at the Army Medical School in Washington and at the Medical Field Service School, Carlisle Barracks, Pennsylvania. Following his tour of duty in Washington, Colonel Madigan was ordered to the Philippine Islands where he was chief of the neuropsychiatry section at Sternberg General Hospital in Manila for two years. He returned to Walter Reed in 1928, and later was sent to the Canal Zone where he was on duty for four years, returning to the United States in 1936. He was then assigned to the station hospital at Fort Sam Houston, Texas, as assistant executive officer and chief of the neuropsychiatry section.

Colonel Madigan was appointed medical advisor to the Surgeon General in Washington in 1940 and held that post for eight months before assignment as commanding officer of the station hospital at Camp Lee, Va. He remained there until his transfer to Fort Belvoir in February of this year.

Colonel Madigan was a Fellow of the American College of Physicians and of the American Medical Association.

He leaves his wife, Mrs. Mary Shugree Madigan; two sons, Emmet P. Madigan, a first lieutenant in the Army Medical Corps and Gerald P. Madigan, a student at Georgetown Preparatory School; two brothers, Colonel John J. Madigan, also of the Army Medical Corps, Dr. Joseph P. Madigan; and three sisters, Misses Margaret and Mary Madigan and Mrs. A. Levin, all of Washington.

MAJOR GENERAL NORMAN T. KIRK, (MC), USA,
A.C.P. Governor for the U. S. Army

DR. CLARENCE JAMES MCMULLEN

Dr. Clarence James McMullen, Fellow of the American College of Physicians since 1940, died May 25, 1944, at the age of 54.

Dr. McMullen was born at Des Moines, Iowa, in 1890, and received his early education in Chicago, Ill. He graduated from Illinois College of Medicine in 1912, and took a postgraduate course in cardiology under Dr. Paul D. White at the Massachusetts General Hospital. From 1914 to 1926 he served as Instructor and subsequently as Associate Professor of Medicine at the University of Illinois College of Medicine. The ensuing two years were spent at Rush Medical College, Chicago, where he was Assistant Professor of Medicine. For 15 years, between 1923 and 1938, Dr. McMullen was Attending Physician at Cook County Hospital, Chicago, where he also became Consulting Physician on diabetes.

In addition to being a Fellow of the American College of Physicians, he was a member of the Chicago Medical Society, Chicago Society of Internal Medicine, and the American Medical Association.

Failing health cut short a promising career at the age of 48, and Dr. McMullen died a few years following his retirement to Los Angeles, California.

ROY E. THOMAS, M.D., F.A.C.P.,
Governor for Southern California